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THE EFFECT OF INCREASED INTRACRANIAL VENOUS PRESSURE ON THE PRESSURE OF THE CEREBROSPINAL FLUID.

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IT has been known for some time that constriction of the veins of the neck is followed by an increase in the pressure of the cerebrospinal fluid. This phenomenon was made use of by Queckenstedt [13] in his test for obstruction of the spinal subarachoid space. Queckenstedt suggested that the rise in the pressure of the cerebrospinal fluid was due to an over-filling of the brain with blood. He thought also that the pressure was perhaps raised in another way. He believed that after compression of the veins of the neck blood escaped from the brain into the venous plexuses which surround the dural coverings of the spinal cord. The vessels of these plexuses would then become distended with blood and exert an abnormal pressure on the dura of the upper cervical cord. This he thought would lead to an increase in the pressure of the cerebrospinal fluid. It is noteworthy that Queckenstedt found it unnecessary to postulate either an increased formation or a delayed absorption of the cerebrospinal fluid to account for the rise of pressure.

Before considering the effect of increased intracranial venous pressure on the pressure of the cerebrospinal fluid it is proposed to consider briefly what is known of the normal relation of the intracranial venous pressure and the cerebrospinal fluid pressure.

The normal relation of the intracranial venous pressure and the cerebrospinal fluid pressure.

The experimental investigation of the subject may be said to have started with the work of Leonard Hill [12] in 1896. Hill attempted to make direct measurements of the two pressures and came to the

conclusion that the cerebrospinal fluid pressure and the torcular venous pressure must at all times be equal. Nearly twenty years later Dixon and Halliburton [7] also made direct measurements of the pressures, and expressed the opinion that the cerebrospinal fluid pressure was independent of the venous pressure at the torcular and that of the two the venous pressure was considerably the higher. Wagefarth [14], about the same time, considered that the cerebrospinal fluid and the torcular pressures were not equal but that the cerebrospinal fluid pressure was normally the greater although it was being constantly reduced towards the level of the venous pressure. He came to these conclusions in the following way. An artificial opening was made between the superior longitudinal sinus and the subarachnoid space in dogs, the opening persisted for at least four days. Bleeding from the sinus into the subarachnoid space occurred in only one case and in this animal cerebrospinal fluid had been removed at the time of the puncture. In these animals the removal of anything but the smallest amount of cerebrospinal fluid was followed by marked subdural and subarachnoid hæmorrhage. These experiments would seem to indicate that the cerebrospinal fluid pressure was constantly above that of the superior longitudinal sinus and that blood did not pass from the sinus to the subarachnoid space unless cerebrospinal fluid was withdrawn in a quantity sufficient to alter the intracranial pressure relations.

Frazier and Peet [11] considered that the torcular and the fluid pressures were identical and thus supported the findings of Leonard Hill. A careful investigation of the problem was made by Becht [1] who came to the conclusion that the torcular and the cerebrospinal fluid pressures were almost but not exactly equal and that no definite statement could be made as to which pressure was normally the higher. Weed and Hughson [15], however, by employing an improved method of recording the torcular venous pressure came definitely to the conclusion that "the pressure of the cerebrospinal fluid is not identical with either the sagittal or the brachial venous pressure." They also stated that "in the control experiments and in the initial control periods of other observations, the cerebrospinal fluid pressure has been found to be from 5 to 50 mm. above that of the sinus" and they concluded that under normal conditions the pressure of the cerebrospinal fluid was always higher than the torcular pressure.

In the experiments which are about to be described it was the custom to measure both the torcular and the cerebrospinal fluid pressure during an initial control period. The animals were always in the

horizontal position. Although observations were made on many dogs, the torcular pressure was always found to be from 25 to 95 mm. of a 4 per cent. solution of sodium citrate below that of the cerebrospinal fluid.

These observations confirm the finding of Weed and Hughson that the pressure of the cerebrospinal fluid always exceeds that of the torcular, but it should be noted that the difference in the two pressures was occasionally found to be greater than the maximum described by these two workers.

We are now in a position to consider what is known of the effect of obstruction of the venous return from the brain on the pressure of the cerebrospinal fluid.

The effect of obstruction of the venous return from the brain on the pressure of the cerebrospinal fluid.

According to Becht [1], who has reviewed the literature up to 1920, Falkenheim and Naunyn [9] were the first to study the effect of raising the venous pressure on the pressure of the cerebrospinal fluid. A small rubber balloon was placed in the right ventricle of the heart and inflated. In two animals there was a rise in the pressure of the cerebrospinal fluid while in the third animal there was a fall. Falkenheim and Naunyn concluded that the rises in fluid pressure were caused by venous stasis without much reduction in the arterial pressure while the fall was caused by a fall in the arterial pressure due to the marked reduction of cardiac output which was caused by the direct pressure of the balloon. Dixon and Halliburton [7] observed in the course of their experiments that a rise of venous pressure caused a rise in the pressure of the cerebrospinal fluid. They also found that the rise in the pressure of the cerebrospinal fluid was only about one quarter of the rise in the pressure at the torcular. They found, however, that the alterations in the fluid and the venous pressures were neither synchronous nor proportional and they concluded that although the pressure of the cerebrospinal fluid was influenced to a small extent by changes in the venous pressure these alterations were insignificant compared with the independent changes in pressure which occurred as the result of secretory activity. Frazier and Peet [11] found that a fairly constant rise in the pressure of the cerebrospinal fluid followed occlusion of the venous circulation. They concluded that "the more or less constant rise in cerebrospinal fluid pressure when the venous circulation is interrupted confirms the hypothesis that the absorption of cerebrospinal fluid takes place chiefly

through the venous channels." A series of experiments was performed by Dandy and Blackfan [5] on dogs, in which they noted the rate of escape of cerebrospinal fluid from a needle in the cisterna magna. They observed an instantaneous and marked increase in the outflow of cerebrospinal fluid on compressing the jugular veins. They state: "This increased production (of cerebrospinal fluid), however, disappears within a few minutes as the collateral venous circulation becomes established" and later they express the opinion that the increased outflow of cerebrospinal fluid can be explained only by an increased production of fluid.

Much of our knowledge of the nature of the initial effects of compression of the jugular veins upon the pressure of the cerebrospinal fluid is due to the work of Becht [1]. This worker's experiments provide fairly conclusive evidence that the sudden increase in the pressure of the cerebrospinal fluid which follows compression of the vessels of the neck is caused neither by an increased production nor by a delayed absorption of the cerebrospinal fluid, but that it is due to an accumulation of venous blood in the cranial cavity and a displacement of the cerebrospinal fluid into the spinal canal. Becht came to these conclusions as a result of the following observations: (1) He found that the changes in the fluid and the torcular pressures observed on compression and on release of the veins of the neck varied in the same direction and ran a remarkably parallel course. It was evident from these observations that one of the factors which determined the pressure of the cerebrospinal fluid was the venous pressure in the skull. (2) He raised the pressure of the cerebrospinal fluid to a constant height: (*a*) By introducing saline solution into the subarachnoid space through a needle in the cisterna magna; (*b*) by a temporary ligation of the external jugular veins. He then determined the time required for the pressures to return to their original levels. The time required for the fall of pressure after the introduction of saline was nearly thirty times as long as that after release of the jugular veins. Further, the rise of pressure in the former instance was unaccompanied by a rise in the pressure at the torcular while in the latter it was accompanied by an increase in the torcular pressure. In one of his experiments, six minutes were required before the pressure of the cerebrospinal fluid which had been raised by the introduction of saline solution returned to its original level while a pressure of equal height which had been produced by constriction of the external jugular veins returned to its original level in eleven seconds when these vessels were released. Becht considered that if an actual increase in the quantity of cerebro-

spinal fluid had resulted from ligation of the jugular veins, a longer period than eleven seconds would have been required for readjustment after release of the veins. Becht's observations on the effect of ligation of the jugular veins on the pressure of the cerebrospinal fluid have been confirmed and extended by Weed and his co-workers. Weed's [16] conclusions are summarized in the following extract from a paper entitled "The relation of the intracranial pressures" which he published in collaboration with Flexner in 1933: "Increase in the cerebral venous pressure as effected by pressure upon the veins of the neck of the animal results in a prompt rise in the pressure of the cerebrospinal fluid but always to a lesser extent (than the rise in venous pressure). Eleven experiments in our series yielded an average increase of 267 mm. in cerebral venous pressure and 176 mm. in cerebrospinal fluid pressure, indicating that 65 per cent. of the venous pressure increase is reflected in the pressure of the fluid. If, however, the data are taken from levels at which the pressure of the cerebrospinal fluid is raised but slightly over 100 mm. (as in the case of head-down tilting), the average increase becomes 178 mm. for the sagittal sinus and 112 mm. for the cerebrospinal fluid. Hence within this normal range of pressure-change, 63 per cent. of a sagittal pressure increase is reflected upon the cerebrospinal fluid." Weed, however, was mainly concerned with the investigation of the factors responsible for the changes in cerebrospinal fluid pressure which occur on the abrupt alteration of the animal's position. It is not proposed to consider this aspect of the subject in this communication.

With the possible exception of Dandy and Blackfan, the investigators whose work has just been described appear to have been concerned mainly with the effect on cerebrospinal fluid pressure of a sudden and temporary occlusion of the veins of the neck and to have made little attempt to determine the effect of prolonged venous obstruction. Allusion has already been made to Dandy and Blackfan's experiments. Their conclusions have been severely criticised by Becht [1] and by Weed [15] who have pointed out that their experimental findings can readily be explained without postulating a new formation of cerebrospinal fluid. Similarly their conclusion that the falling off of the initial outflow of fluid which was found to occur during prolonged compression of the jugular veins coincided with the establishment of collateral circulation, appears to have been mainly speculative, for they record no measurements of the intracranial venous pressure.

In a paper which appeared in 1919, Dandy [6] re-stated his views in the following terms: "Whether hydrocephalus results from venous

stasis depends entirely upon the amount of collateral circulation which can develop. If both jugular veins are compressed in a dog, the amount of cerebrospinal fluid is immediately and rapidly increased. The increased production, however, disappears within a few minutes as the collateral circulation becomes established." Flexner and Winters [10] determined the rate of flow of cerebrospinal fluid from the aqueduct of the cat. They maintained the cerebrospinal fluid at a constant pressure of 110 mm. water throughout the experiments. In several of the experiments the cerebral venous pressure was also recorded by a cannula in the peripheral end of an external jugular vein. Certain deviations from a constant rate of flow of cerebrospinal fluid were correlated with intracranial venous pressure changes and were considered to provide evidence of changes in the ventricular volume. No observations, however, are recorded of the influence of a prolonged increase of intracranial venous pressure on the flow of cerebrospinal fluid.

Although the effect on the cerebrospinal fluid pressure of an abrupt and temporary increase in the intracranial venous pressure seems now to have been determined with accuracy, little or no work is available concerning the influence of a prolonged state of raised intracranial venous pressure. It may, indeed, be claimed that although the initial rapid rise in the pressure of the cerebrospinal fluid is caused by an increase in the volume of the intracranial venous system and not by an increase in the quantity of the cerebrospinal fluid, a prolonged state of raised intracranial venous pressure may nevertheless lead to the accumulation of cerebrospinal fluid. This could be effected in one or both of the following ways: (*a*) the raised intracapillary pressure of the choroid plexuses may lead to an increased filtration of cerebrospinal fluid if simple filtration is the process by which cerebrospinal fluid is normally formed; (*b*) the raised blood-pressure in the intracranial venous sinuses may cause a delay in the rate of absorption of the cerebrospinal fluid and provided the rate of formation remains constant cerebrospinal fluid may tend to accumulate in the subarachnoid space. A criticism of the first of these possibilities has been presented in an earlier paper [2]. It is apparent, however, from the following extracts, which are taken from "Recent Advances in Neurology" (1934), by Brain and Strauss, that both these views are not lacking in supporters. On page 8 the authors state: " . . . a general rise of intracranial venous pressure, however, is a frequent accompaniment of cerebral tumour and this may contribute to the development of hydrocephalus by leading to an increased formation of cerebrospinal fluid, since a

general rise of intracranial venous pressure would involve not only the vein of Galen but also its collaterals," and later on page 12: "An abnormally high blood-pressure in the intracranial venous sinuses diminishes the absorption of cerebrospinal fluid by increasing the force opposing the passage of the fluid through the arachnoid villi. A cerebral tumour which presses upon venous sinuses may thus in yet another fashion contribute to the development of hydrocephalus."

The experiments which are to be described were undertaken in an attempt to determine the influence of a prolonged state of increased intracranial venous pressure upon the pressure of the cerebrospinal fluid. As it was necessary in some of the experiments to place obstructions on the course of the intracranial venous sinuses, it is proposed first to describe the anatomy of the intracranial venous system of the dog.

The intracranial venous system of the dog.

A search through the available literature has failed to reveal any account of the intracranial venous system of the dog other than that by Ellenberger and Baum [8]. As the description given by these authors was found to be incomplete and to contain a number of inaccuracies it was decided to restudy the whole system. For this purpose a number of dogs' heads were prepared for dissection by the injection of the venous system with carmine gelatine solution. The method employed has already been described in an earlier paper [3].

Almost the whole of the blood from the convexity and the greater part of the blood from the inner aspect of the cerebral hemispheres drain into the superior longitudinal sinus. It will be observed from fig. 1 that the sinus, on reaching the torcular Herophili, divides its blood equally between the right and the left lateral sinuses. Just before terminating the superior longitudinal sinus enters a canal in the substance of the occipital bone. The torcular and the inner third or more of the lateral sinuses are also situated within the bone. The straight sinus enters the torcular through a foramen in the upper part of its anterior wall. For details of the Galenic system of the dog reference should be made to an earlier paper [2]. The lateral sinus follows a course which corresponds fairly closely with that found in man until it reaches the posterior border of the petrous portion of the temporal bone. Here the sinus runs forwards and downwards in the substance of the temporal bone and emerges from the skull through the postglenoid foramen which is situated directly behind the postglenoid process.

Ellenberger and Baum have applied the term "superior cerebral vein" to the sinus after it has left the skull. It is soon joined, however, by the internal maxillary vein and the common trunk so formed unites with the external maxillary vein to form the external jugular vein. The arrangement of the veins in this region is, however, very irregular

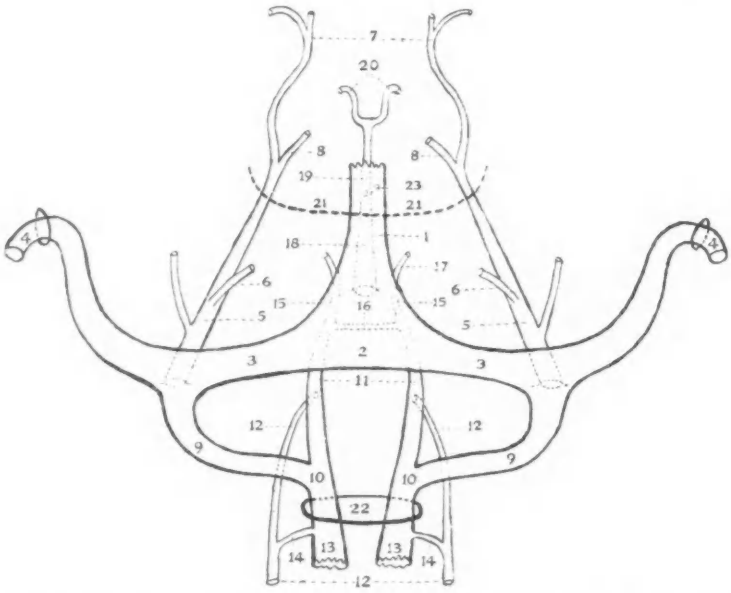

FIG. 1.—Diagrammatic representation of the intracranial blood-sinus system of the dog. The true relations of the various structures have been considerably distorted and the sinuses are depicted as occupying one plane. (1) Superior longitudinal sinus; (2) torcular of Herophili; (3) lateral sinus; (4) postgleniod foramen; (5) basal vein; (6) temporo-occipital tributary of basal vein; (7) anterior cerebral vein; (8) tributary from medulla, pons and cerebellum; (9) superior occipital sinus; (10) inferior occipital sinus; (11) petrosal sinus; (12) internal jugular vein; (13) vein of vertebral column; (14) tributary of internal jugular vein from vein of vertebral column; (15) cavernous sinus; (16) intercavernous sinus; (17) ophthalmic vein; (18) straight sinus; (19) great vein of Galen; (20) vein of Galen; (22) foramen magnum; (21) tentorium cerebelli; (23) inferior longitudinal vein.

and a detailed description is unnecessary for the purposes of this communication. It is, of course, well known that in the dog the external jugular vein is a large and well-defined vessel and contrasts with the internal jugular vein which is relatively small. In the dog there is no sigmoid sinus and although Ellenberger and Baum have described a superior petrosal sinus this has not been encountered in any of the specimens which have been examined. Just before the lateral sinus

reaches the posterior border of the petrous temporal bone, a venous sinus passes directly downwards from its lower border. This is the superior occipital sinus. At first the sinus lies within the dura but it soon enters a canal in the occipital bone and ultimately unites with the petrosal sinus to form the inferior occipital sinus. The anterior wall of that portion of the lateral sinus from which the superior occipital sinus takes origin is not usually ossified. An opening through which blood is received from the basal vein is situated in the region where the superior occipital sinus takes origin. A detailed description of this vessel has been presented in an earlier communication [9]. The basal vein receives blood mainly from: (1) the under surface of the optic lobe through the anterior cerebral vein; (2) the under surface of the temporal and occipital lobes through a large vessel which usually joins the basal vein while the latter lies within the tentorium; (3) a proportion from the island of Reil, the midbrain, the pons, the cerebellum and the choroid plexus of the descending horn. The main function of the vessel, however, appears to be the drainage of blood from the inferior aspect of the cerebral hemispheres. It is noteworthy that the opening where the basal vein terminates in the sinus is horizontal and slit-like and immediately above it is a fold of dura which corresponds with the floor of the lateral sinus. While it is difficult to be certain of the function of this fold of dura, which varies considerably in size from specimen to specimen, it would appear to serve the purpose of directing the blood from the basal vein into the superior occipital sinus. In a previous communication the basal vein has been described as terminating in the lateral sinus; it would perhaps be more correct to describe it as terminating in the superior occipital sinus. It must be admitted, however, that no direct evidence could be obtained of the normal direction of blood flow in the superior occipital sinus and although it seems reasonable to presume that it is downwards towards the inferior occipital sinus it is conceivable that under certain circumstances the flow may be in a reverse direction towards the lateral sinus.

The cavernous sinus receives its blood mainly from the orbit through the ophthalmic veins. Although Ellenberger and Baum describe veins entering the sinus from the cerebral hemispheres, it has been impossible to demonstrate them. The anterior intercavernous sinus is not represented in the dog. The posterior intercavernous sinus, however, is a well-defined structure. The spheno-parietal and the superior petrosal sinuses are also absent in the dog. The petrosal sinus runs backwards from the posterior end of the cavernous sinus in a bony canal, situated

between the petrous temporal bone and the basiocciput. The sinus then enters a canal in the substance of the occipital bone where it unites with the superior occipital sinus to form the inferior occipital sinus. A vein passes from the petrosal sinus to the exterior through the foramen lacerum posterius. This vessel is the beginning of the internal jugular vein. The inferior occipital sinus is a very short sinus. It runs backwards and inwards in the interior of the bone and opens on the inner aspect of the condylar portion of the occipital bone. It then passes through the foramen magnum and becomes the vein of the vertebral column. The veins of the vertebral column are large vessels which are continuous throughout the whole vertebral column. In the cervical region they resemble sinuses. They are situated outside the dura, but within the periosteum, and occupy a groove on either side of the posterior longitudinal ligament. They are in frequent communication with each other and receive blood from the spinal medulla and the vertebræ. A vessel also passes to the exterior through each intervertebral foramen. In this way they are brought into communication with the veins of the neck, the intercostal, the lumbar and the sacral veins.

As already stated, the internal jugular vein in the dog is normally a very small vessel. It starts as a small branch from the petrosal sinus which passes through the foramen lacerum posterius. This venule is very soon joined by a somewhat larger vessel from the upper part of the vein of the vertebral column. Occasionally the internal jugular vein is not represented by a single trunk, but by a small plexus of veins which lies along the course of the internal carotid artery.

To summarize, it would appear that blood from the convexity and the greater part of the inner aspect of the cerebral hemispheres and also the bulk of the blood from the interior of the brain find their way to the torcular. After leaving the torcular two routes are available. Blood may leave the cranium through the lateral sinuses and the external jugular veins. This appears to be the normal route. On the other hand, some blood may escape through the superior occipital sinuses and ultimately find its way into the veins of the vertebral column. It would seem probable that the blood from the greater part of the under surface of the cerebral hemispheres and some of the blood from the mid-brain, the pons, and the cerebellum which drain into the basal veins normally leave the cranium through the latter route. Some blood also escapes from the petrosal sinuses into the internal jugular veins.

We are now in a position to consider the effect of experimental

obstruction of the venous return of the brain upon the pressure of the cerebrospinal fluid.

I.—The Effect of Obstruction of the External Jugular Veins upon the Pressure of the Cerebrospinal Fluid.

Experimental technique.—Short-haired dogs of the mongrel type which weighed from 7 to 8 kg. were the animals of choice. Reliable results can only be obtained if the animals are strong and in good health. Anæsthesia was first induced by the ether bomb and maintained by intratracheal insufflation. Care is required to maintain the rate of administration as near constant as possible. An abrupt change in the concentration of the ether is followed immediately by changes in the arterial, venous and cerebrospinal fluid pressures. Although an injection of morphia rendered the administration of ether much less difficult, it was found to have a disturbing effect on the pressures which became unsteady, and it was accordingly avoided. Similar observations have been made by Becht [1] and by Weed and Hughson [15]. The animals were maintained in the horizontal position with the head raised slightly above the rest of the body and supported on a block of wood. It was the custom to record a pressure-reading only after it had remained reasonably steady for a period of not less than ten minutes. The cerebrospinal fluid pressure was recorded with a 1 mm. bore straight manometer attached to a needle in a cisterna magna.

The venous pressure at the torcular was recorded in the following way. A quarter-inch trephine hole is made over the superior longitudinal sinus about a quarter of an inch in front of the point where the sinus enters the torcular. The sinus appears as a dark band at the bottom of the trephine hole. The wall of the anterior part of the trephine hole is then trimmed with bone forceps and made to slope. With the aid of a fine needle a small puncture is made into the sinus and a larger short bevelled needle (gauge 18) is then passed through the puncture hole down towards the torcular. This needle is then attached to a 1 mm. bore straight manometer containing a 4 per cent. solution of sodium citrate. Finally the trephine hole is sealed with wax. Care is needed in the choice of the needle for recording the venous pressure. With a small bore needle clotting is liable to occur early, while too large a needle may impede the blood flow through the sinus. Weed and Hughson are of the opinion that obstruction to the flow of blood in the superior longitudinal sinus causes a rise in the pressure of the cerebrospinal fluid and they consider that the absence of such a rise when a

needle is introduced into the sinus indicates that there is no obstruction to the blood flow. In none of the experiments which are to be described was a rise in cerebrospinal fluid pressure observed to follow the introduction of the needle. In any case, it is doubtful if the presence of a gauge 18 needle in the posterior end of the superior longitudinal sinus of an 8 kg. dog is likely to cause an obstruction of any consequence. In order to diminish the risk of clotting the following precautions were taken: (1) the needle used for recording the pressure was short bevelled and blunt so as to reduce the risk of injuring the sinus endothelium. (2) Previous to insertion the needle was carefully dried with absolute alcohol and ether and then heated for about ten minutes in liquid paraffin. (3) The manometer contained a 4 per cent. solution of sodium citrate. With careful attention to detail the risk of clotting can be considerably reduced.

Although various degrees of increased intercranial venous pressure can be brought about very conveniently by tying a loop round the animal's neck, this method was found to be unsatisfactory for the purposes of these experiments. It was soon discovered that the swelling of the neck which resulted from this procedure caused the constricting band to exert a gradually increasing pressure on the vessels of the neck. Under these circumstances the venous pressure at the torcular continued to rise as the degree of venous obstruction gradually became more complete. It was decided, therefore, to apply a local constriction to the external jugular veins. In order to achieve this the veins were exposed at the level of the upper part of the trachea and ligatured with catgut. In acute experiments, when it was sometimes necessary to release the vessels rapidly, small clips were placed on the veins. When this method was employed the venous pressure at the torcular reached its maximum almost at once, although it never rose to the heights which were attained when a constricting band was applied to the whole neck.

A record of the arterial pressure was obtained by means of a cannula in the femoral artery. The pressure was not recorded at the common carotid artery as it was considered desirable to avoid as far as possible any interference with the arterial supply of the brain. An experiment was not considered successful unless the systolic blood-pressure remained steady throughout the period of observation. Weed and Hughson [15] state that "Minor slow alterations of the cerebral arterial supply as determined by the carotid pressure seem to have no appreciable effect upon the pressure of either the cerebrospinal fluid or the sagittal sinus tension. Marked sudden alterations in the arterial supply to the

structures within the cranial cavity, however, do affect the pressures of the cerebrospinal fluid and superior sagittal sinus—a conclusion held by Dixon and Halliburton and by Becht. This influence of arterial supply, is, however, of apparently less physiological importance than is venous pressure."

In the experiments which are about to be described it was found that minor slow alterations in the arterial blood-pressure had normally little influence upon the cerebrospinal fluid and the torcular venous pressures. When, however, the intracranial venous pressure had been raised by ligation of the external jugular veins the cerebrospinal fluid and the torcular venous pressures were found to be much more sensitive to changes in the arterial blood-pressure. It was necessary, therefore, to have a continuous record of systemic blood-pressure in all experiments dealing with the effect of raised intracranial venous pressure upon the pressure of the cerebrospinal fluid.

(1) *The normal relation of the intracranial venous pressure and the cerebrospinal fluid pressure.*

Table I is a record of the torcular venous pressure, the cerebrospinal fluid pressure and the arterial pressure at the femoral artery in fourteen dogs. The pressures were recorded simultaneously and were obtained

TABLE I.—THE RELATION OF THE CEREBROSPINAL FLUID PRESSURE AND THE INTRACRANIAL VENOUS PRESSURE IN FOURTEEN DOGS.

Experiment No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1	95	60	110
2	150	89	115
3	135	65	90
4	130	80	130
5	100	35	120
6	110	50	115
7	125	70	105
8	120	60	95
9	135	110	105
10	90	20	115
11	100	75	125
12	120	65	105
13	110	80	100
14	125	30	135

The cerebrospinal fluid pressure is recorded in millimetres or normal saline solution and the torcular venous pressure in millimetres of 4 per cent. sodium citrate solution.

during the initial control period of experiments for different purposes. A pressure reading was recorded only when the excursion of the column of fluid in the manometer was of normal amplitude and remained reasonably steady for not less than ten minutes. It will be observed that in these experiments the venous pressure at the torcular never exceeded

that of the cerebrospinal fluid. Considerable variation in the height of the venous pressure was observed from animal to animal. In three experiments it was found to be less than 40 mm. of a 4 per cent. solution of sodium citrate. There was no reason to believe that these low readings were the result of errors of technique for in each instance the excursion of the column of fluid in the manometer recording venous pressure was of normal amplitude and the pressure rose and fell normally on temporary compression of the external jugular veins.

(2) *The effect of a temporary occlusion of the external jugular veins.*

Table II is a record of the effect of ligation of the external jugular veins upon the pressure of the cerebrospinal fluid and the venous pressure at the torcular in six dogs. The cerebrospinal fluid pressure and the torcular venous pressure attained their maximum height simultaneously and a few seconds after the veins were occluded. It will be observed that the two pressures may rise to very nearly the same level. In some experiments, however, the level reached by the venous pressure was the higher,

TABLE II.—THE EFFECT OF TEMPORARY OCCLUSION OF THE EXTERNAL JUGULAR VEINS UPON THE CEREBROSPINAL FLUID AND THE TORCULAR VENOUS PRESSURES.

Experiment No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1*a*	95	60	110
b	210	195	110
2*a*	150	89	115
b	230	210	115
3*a*	135	65	95
b	255	270	90
4*a*	130	80	130
b	230	280	130
5*a*	100	35	120
b	200	195	120
13*a*	110	80	100
b	190	210	100

a. Pressures before occlusion. *b*. Pressures after occlusion. The cerebrospinal fluid pressure is recorded in millimetres of normal saline solution and the torcular venous pressure in millimetres of 4 per cent. sodium citrate solution.

while in other experiments the cerebrospinal fluid pressure exceeded the venous. The average proportion of the venous increase of pressure which was reflected in the pressure of the cerebrospinal fluid was 61 per cent. This figure is identical with that obtained by Becht [1]. Occlusion of the external jugular veins was usually found to have no influence on the femoral arterial pressure. Occasionally, however, it was accompanied by a slight but temporary fall of blood-pressure. On release of the jugular veins the cerebrospinal fluid pressure and the

venous pressure at the torcular returned to their original levels within a few seconds. Not infrequently, however, lower levels were first assumed and then the pressures rose gradually to the original level. These observations are on the whole in harmony with the findings of Becht [1] and of Weed and Hughson [15].

(3) *The effect of prolonged occlusion of the external jugular veins.*

An attempt was now made to determine the effect of a prolonged occlusion of the external jugular veins. In a number of dogs the anæsthesia was maintained for two to three hours and a reading of the pressures was taken at intervals of five minutes. The results of an average experiment are indicated in fig. 2. The cerebrospinal fluid

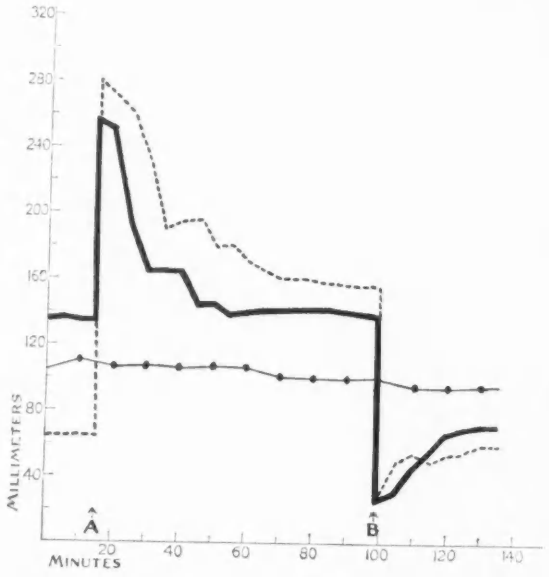

FIG. 2.—The effect of occlusion of the external jugular veins upon the cerebrospinal fluid pressure and the venous pressure at the torcular. The ordinates represent millimetres of normal saline solution or of mercury. The veins were occluded at A and released at B.

Cerebrospinal fluid pressure : ——————
Venous pressure at the torcular : - - - - - - -
Systolic pressure at femoral artery : —●–·–●—

and the torcular venous pressures both begin to fall very soon after they have attained their maximum height. The cerebrospinal fluid pressure at first falls rapidly and then more gradually. The fall often

takes place in a step-like manner. A level approximating the original one before the veins were ligatured is usually attained after thirty to forty-five minutes. The pressure then remains steady or continues to fall somewhat below its original level. The fall in the venous pressure is not so rapid or complete. In this experiment it will be observed that by the time the cerebrospinal fluid has attained a pressure which reasonably corresponds to the original one before the veins were ligated, the venous pressure is still nearly three times its original height. In some experiments a much higher venous pressure was found at this point while in others the fall had been more rapid and complete. If the experiments were continued the venous pressure usually became steady, although at a variable height above its original level. It will be observed that in this experiment the cerebrospinal fluid pressure had attained its original level after forty-five minutes, although the venous pressure was not less than three times its original height during almost the whole of this period. The external jugular veins were released one hour and a half after ligation. It will be noticed that the cerebrospinal fluid and the torcular pressures both fell at once to very low levels and that the pressures then rose gradually towards their original levels. On cessation of the experiment thirty-five minutes later, the venous pressure had attained its original level while the cerebrospinal fluid pressure was approximately half its original height.

To summarize, it would appear that the rise in cerebrospinal fluid pressure and in the venous pressure at the torcular which follows ligation of the external jugular veins is of temporary duration. The cerebrospinal fluid pressure has usually returned to its original level after thirty to forty-five minutes. It is noteworthy that this fall often takes place while the venous pressure is several times its original height. The fall in the venous pressure is not so rapid and is often incomplete after several hours. Release of the veins is always followed by a sudden fall of both pressures to very low levels and by a gradual return towards the original level.

II.—The Effect of Obstruction of the Lateral Sinuses upon the Pressure of the Cerebrospinal Fluid.

Having determined the effect of ligation of the external jugular veins upon the pressure of the cerebrospinal fluid and the venous pressure at the torcular, it was considered desirable to devise if possible some method by which the torcular venous pressure could be raised and

maintained at a higher level than that which follows ligation of these vessels. In the hope of achieving this it was decided to occlude the

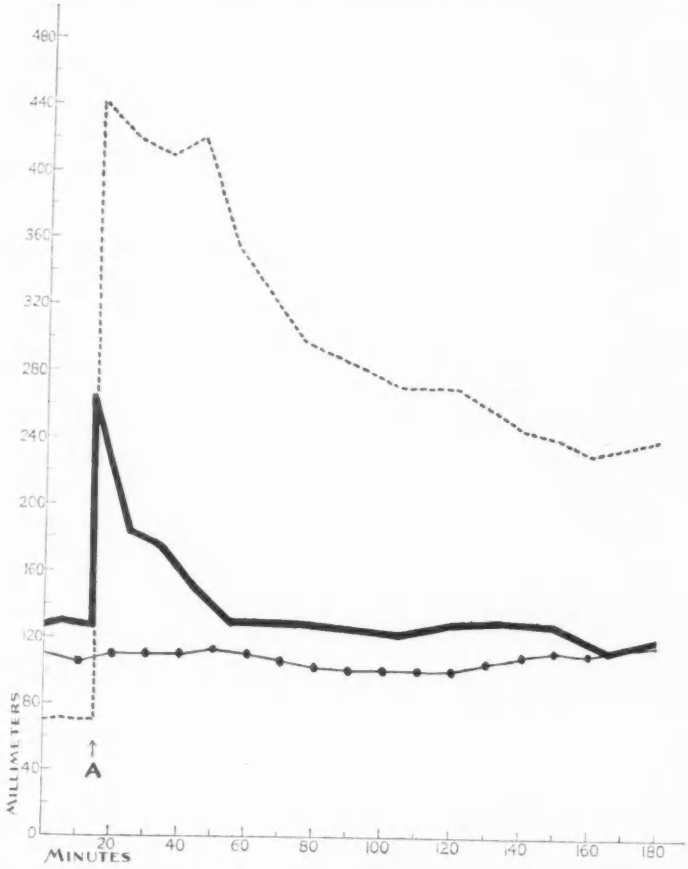

FIG. 3.—The effect of occlusion of the lateral sinuses upon the cerebrospinal fluid pressure and the venous pressure at the torcular. The ordinates represent millimeters of normal saline solution or of mercury. The lateral sinuses were occluded at A.

Cerebrospinal fluid pressure :
Venous pressure at the torcular :
Systolic pressure at femoral artery :

lateral sinuses midway between the torcular and the point at which they are joined by the basal veins (see fig. 1).

Experimental technique.—The bone over the inner third of a lateral sinus was exposed by reflecting part of the temporal muscle. A

quarter-inch trephine hole was then made over the lateral sinus about half an inch external to the torcular. The trephine hole was made in such a way that it did not extend below the lower border of the sinus. If this precaution were not taken subtentorial bleeding was very liable to occur. It was desirable, if possible, to expose the sinus without opening it and to occlude it by compressing with wax. By this means, the risk of clotting was greatly reduced. Often, however, the sinus was unavoidably injured by the trephine and it was necessary to occlude it by introducing wax into the lumen. The anterior wall of the lateral sinus in this part of its course is usually ossified and with ordinary care it is easy to avoid compressing the brain with the wax. Obstruction of one sinus alone had little influence on either the venous or the cerebrospinal fluid pressures. On terminating an experiment a careful post-mortem examination was made to verify the position and the extent of the obstructing mass. It was also necessary to determine to what extent clotting had occurred and to exclude the presence of intracranial hæmorrhage.

The results of a fairly typical experiment are illustrated in fig. 3. It will be observed that although the rise in the pressure of the cerebrospinal fluid which follows obstruction of the lateral sinus only slightly is above the level obtained when the external jugular veins are ligatured, the torcular venous pressure rises to a much higher level. In this experiment only 38 per cent. of the venous rise in pressure is reflected in the rise of cerebrospinal fluid pressure. The average finding for six experiments was 42 per cent. This contrasts with the finding after ligation of the external jugular veins when 61 per cent. of the venous rise of pressure was found to be reflected in the cerebrospinal fluid pressure rise. On the whole the general character of the rise and the fall in the pressures resembles that which follows ligation of the external jugular veins. In this experiment the cerebrospinal fluid pressure has returned to a level within 5 mm. of the original level forty minutes after the sinuses have been occluded. At this time the torcular venous pressure is still five times its original height.

To summarize, it would appear that: (1) The pressure changes which follow occlusion of the lateral sinuses bear a general resemblance to those which follow ligation of the external jugular veins; (2) although the rise in pressure of the cerebrospinal fluid is only slightly higher than that which follows ligation of the external jugular veins, the rise in venous pressure is much greater. A smaller percentage of the venous rise of pressure is reflected in that of the cerebrospinal fluid; (3) the

cerebrospinal fluid pressure has generally returned to its original level after thirty to forty-five minutes although the venous pressure may still be several times its original height.

Discussion.

It would appear from these experiments that the increase in the cerebrospinal-fluid pressure which follows occlusion of the external jugular veins or of the lateral sinuses of the dog is a temporary phenomenon. When the cerebrospinal-fluid pressure has returned to its original level, the torcular venous pressure is still frequently several times its original height. This is most evident when the lateral sinuses have been obstructed. In these experiments a normal cerebrospinal-fluid pressure was frequently found to be present, while the torcular venous pressure was five or more times its original height. The sudden rise of cerebrospinal-fluid pressure which follows venous obstruction is, as has already been indicated, generally regarded as being due to the direct influence of the raised intracranial venous pressure upon the cerebrospinal-fluid pressure, and is not considered to provide evidence of increased cerebrospinal-fluid formation. The experiments which are now under consideration would appear to indicate that a high torcular venous pressure of several hours' duration is not followed by an increased formation of cerebrospinal fluid. The great vein of Galen is the main route by which blood leaves the choroid plexuses of the lateral and of the third ventricles. The great vein of Galen terminates in the straight sinus, which in turn passes its blood directly into the torcular. Although it is impossible to be certain of the effect of pressure changes at the torcular upon the capillary pressure of the choroid plexuses, it is probable that they are closely related. These experiments would seem to indicate that the formation of cerebrospinal fluid is uninfluenced by changes in the venous pressure of the Galenic system, and to favour the view that the process is a true secretion rather than a simple filtration. More evidence is necessary, however, before such a conclusion can be accepted. It might also have been expected that the raised intracranial venous pressure would possibly have interfered with the absorption of the cerebrospinal fluid if this phenomenon is normally one of simple filtration through the cerebral villi. It is obvious, however, from a consideration of the anatomy of the intracranial venous system of the dog that in these experiments the degree of congestion must have been most intense in the superior longitudinal sinus and in the Galenic system. The average duration of the experiments was from two to three

hours; if, however, it had been possible to continue them for longer periods, it is conceivable that results of a different type might have been obtained.

As regards the cause of the fall in the pressures, it would seem probable that the venous pressure falls mainly on account of the development of collateral circulation, and this is responsible indirectly for part of the fall in the pressure of the cerebrospinal fluid. The occurrence, however, of a normal cerebrospinal-fluid pressure in the presence of a torcular venous pressure which is several times its original height, and also the phenomena observed when the external jugular veins are released after an obstruction of several hours' duration, would seem to suggest that there has been an actual decrease in the total volume of cerebrospinal fluid. The greatest caution must, however, be exercised in attempting to interpret intracranial pressure changes in terms of intracranial volume changes, and until it is possible to employ in these experiments a method capable of recording changes in intracranial volume, the interpretation of these findings must remain mainly speculative.

These experiments do, however, appear to have established that: (1) The rise in cerebrospinal-fluid pressure which follows obstruction of the external jugular veins or of the lateral sinuses is a temporary phenomenon, and (2) an abnormally high torcular venous pressure is compatible with a normal cerebrospinal-fluid pressure.

Summary.

(1) The available literature relating to the influence of increased intracranial venous pressure upon the pressure of the cerebrospinal fluid is reviewed.

(2) The anatomy of the intracranial blood-sinus system of the dog is described.

(3) The effect of a temporary ligation of the external jugular veins and also of a ligation of several hours' duration upon the torcular venous pressure and the cerebrospinal-fluid pressure is investigated.

(4) The effect of occlusion of the lateral sinuses is also investigated.

(5) It is concluded that a torcular venous pressure which has been artificially raised to several times its normal height is not accompanied by any sustained change in the pressure of the cerebrospinal fluid in the course of the next two or three hours.

My thanks are due to Mr. S. L. Prescott for assistance during some of the experiments, and to Dr. N. Shtetinin for the drawing.

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VASODILATATION AND VASOCONSTRICTION IN RESPONSE TO WARMING AND COOLING THE BODY: A STUDY IN PATIENTS WITH HEMIPLEGIA.[1]

BY V. UPRUS (TARTU), J. B. GAYLOR (GLASGOW), D. J. WILLIAMS (MANCHESTER), AND E. ARNOLD CARMICHAEL.

In a previous paper attention was drawn to the necessity for observing vasoconstriction rather than vasodilatation as an indication of the functional capacity of the sympathetic nervous system. It is the purpose of this paper to describe a series of investigations appertaining to vasoconstriction and vasodilatation carried out on normal people and on patients suffering from the effects of cerebral lesions, and to discuss the interpretation of the results.

Methods and Material.

The method employed to produce dilatation and constriction was that of immersion of the indifferent limbs in tanks of warm and then of cold water. Simultaneous temperature readings were obtained from the cheeks, and the tips of the digits of the hands and feet by means of thermocouples. Rectal temperature was registered by a thermocouple inserted 5 to 6 cm. above the anal sphincter.

Fifteen normal young post-graduates of both sexes, and twenty-two patients suffering from the effects of isolated lesions of the nervous system, were investigated. Many of these investigations were repeated, the technique being modified to elucidate different points.

It is our privilege here to express our gratitude to the members of the honorary medical staff of the National Hospital who so generously permitted us to carry out these investigations upon patients under their care. To the many post-graduates who willingly offered themselves as controls we extend our thanks.

Results.

A. Normals.—A study of the records obtained from the fifteen normal people shows that following immersion of the feet in water at 44° to 45° C. a simultaneous rise occurred in the temperature of the

[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Uprus held a Rockefeller Foundation Fellowship, and Dr. Gaylor and Dr. Williams Halley-Stewart Research Fellowships.

corresponding fingers. Likewise when the arms were immersed in the warm water the rise in temperature of the toes was simultaneous and equally rapid (fig. 1). On immersing one arm or leg, the temperature of the finger rose before that of the toe. The time interval between the two varied from four to seventeen minutes. Irrespective of the limbs under investigation, the rise in temperature of the cheeks always preceded that of the limbs. In every instance no rise in temperature of digits or cheeks occurred before the rise in rectal temperature.

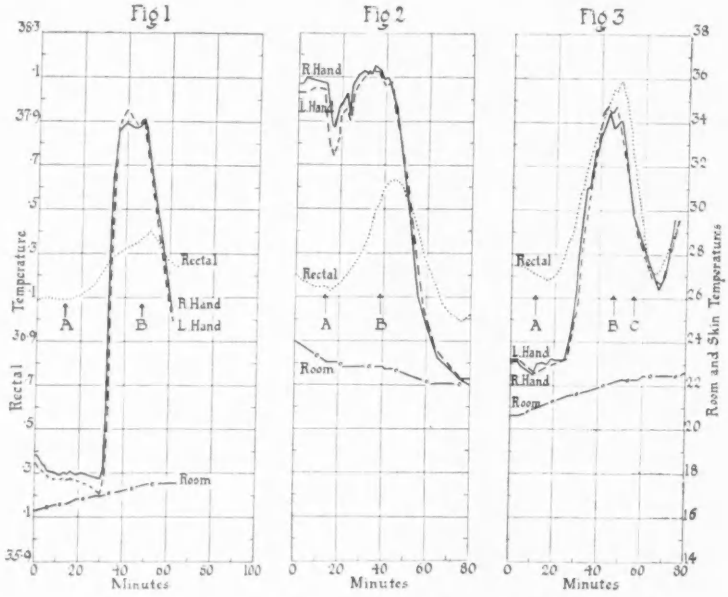

FIG. 1.—A. C., normal. A, feet into water at 45° C.; B, feet into water at 12° C.

FIG. 2.—F., normal. A, feet into water at 45° C.; B, feet into water at 11·5° C.

FIG. 3.—J. L., right hemiplegia. A, feet into water at 44·5° C.; B, feet into water at 11° C.; C, feet into water at 45° C.

In five experiments with different individuals, a fall in the temperature of the digits was observed immediately following the immersion of the legs in hot water. In each, the temperature of the digits was already definitely high. Fig. 2 clearly demonstrates this sequence of events. In only two experiments was a similar fall of temperature of the cheeks observed. The fall in temperature of the fingers was as much as 5° C. in six minutes. A subsequent rapid rise of temperature always took place. This initial fall of temperature was never observed in the feet;

it should be noted that in no case was the temperature of the feet high at the commencement of an experiment.

When the temperature of the digits under examination had reached a nearly stable high level, the indifferent limbs were transferred to tanks of water at 12° to 15° C. Immediately on immersion in cold water, the temperature of the digits of the other limbs began to fall, and in twenty to thirty minutes approximately reached that of the room. Simultaneously with the fall in digital temperature, there was a fall in the temperature of the cheeks. This was not so rapid, nor did it reach so low a level as that of the digits. When thermocouple readings were being taken from the arm and leg, the temperature of the toes fell more rapidly and to a lower level than that of the finger.

Close analysis of the curves of the fall in temperature of the digits showed that for the first minute or two following immersion of the other limbs in cold water, the rate of fall was slow and then rapidly increased. This was more easily observed in the fingers. In two experiments, the initial fall of temperature of the fingers was followed by a slight rise and then a subsequent and more rapid fall of temperature (fig. 2). Synchronous rectal temperature readings demonstrated that the time of onset of this increased gradient or secondary decrease of digital temperature occurred at the same time as the rectal temperature began to fall.

When adequate cooling of the digits had been registered the indifferent limbs were again transferred to warm water. Following this, the rectal temperature continued to fall for several minutes and then began to rise. After the rectal temperature had begun to rise the temperature of the cheeks and then that of the digits rose rapidly. In every way the curve of the skin temperature was similar to that following the earlier immersion in hot water. It differed, however, in its relationship to actual rectal temperature. In every instance the rise in the digital temperature occurred when the rectal temperature was at a lower level than on the first occasion.

These experiments show that in a normal individual the rise in the temperature of the digits of similar limbs is synchronous when the method of immersion is used. Again, it has been shown that the face warms first, then the hand, and lastly the foot. The rise in temperature of the digits only occurs after the rectal temperature has risen, but it is not dependent upon the actual rectal temperature. Following cooling, like digits of two limbs show a similar and synchronous fall of temperature.

Hemiplegia.

A series of twenty-two patients with evidence of involvement of either the motor or sensory functions of one hemisphere were investigated. Of these twenty-two cases, thirteen had vascular lesions and nine tumour growths. The age of the lesion was from 6 days to 10½ years. Cases with lesions situated in each lobe of the hemisphere were examined. Further, patients with cortical and deep lesions were studied. The degrees of dysfunction varied from slight disturbance to an apparently complete loss of function. For instance, the motor defect varied from slight to practically complete loss of voluntary movement; sensory disturbance was minimal in some, and very considerable in others. Many cases were examined on more than one occasion, and patients with cerebral tumour were frequently tested before and after operation.

It was found in this series of cases and on repeated investigations on the same patient that there was no constancy in the temperature differences of the two sides. In several cases with cerebral lesions, the affected side was higher in temperature one day, to be lower than the normal on the next.

Following immersion of the indifferent limbs in tanks of warm water, the temperature of the digits of the two arms or two legs rose simultaneously, and equally rapidly, to reach a maximum in a few minutes. In no case was any delay encountered in the affected limb, nor did the rise of temperature of that limb precede that of the normal. In all cases the rise of temperature of the digits followed the rise in temperature of the rectum (fig. 3).

After adequate warming of the digits had occurred, the indifferent limbs were placed in cold water. Following this procedure the observations made were similar in every way to those in the series of normals. If records were obtained from the fingers, those of both hands cooled equally rapidly (fig. 3). Three exceptions were found to this. In these, compared with those of the normal side, the digits of the affected hand cooled less rapidly, and in a more irregular manner (fig. 4). Observation showed that in each of these cases the affected limb was spastic, and that during the time of cooling there was adduction of the arm with flexion of the fingers and wrist. The irregularity of the fall in the digital temperature on the affected side took place when the limb was moved. In such cases the digits of the lower limb showed a fall in temperature which was equal and regular on the two sides. No alteration in posture of the lower limbs took place during the cooling.

A low temperature of the digits having been produced, the limbs immersed in the cold water were transferred to water at 44° to 45° C. Following this, after the rectal temperature had begun to rise, the temperature of the digits again rose—that of the fingers and toes of each side together.

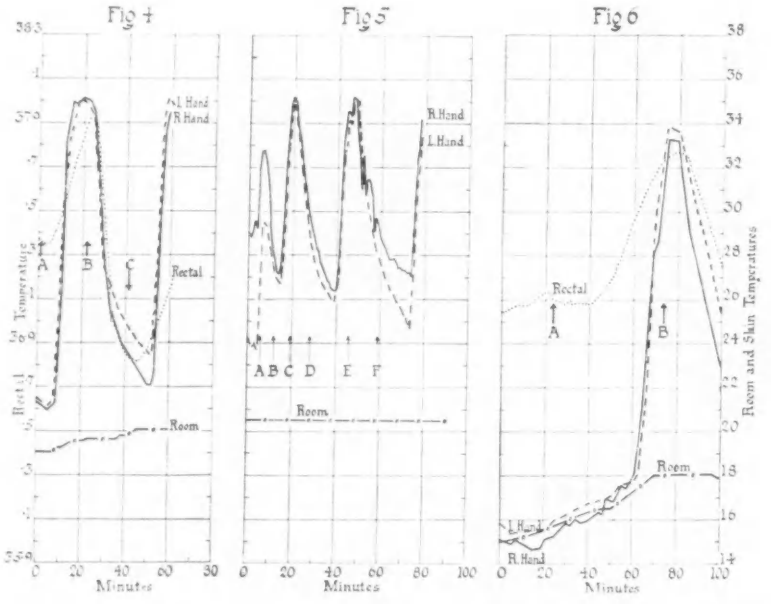

FIG. 4.—E. S., left hemiplegia. A, feet into water at 44·3° C.; B, feet into water at 12·5° C.; C, feet into water at 44·5° C.

FIG. 5.—A. C., normal. A, feet into water at 43° C.; B, water heated to 45° C.; C, feet into water at 10° C.; D, feet into water at 45·5° C.; E, feet into water at 12° C.; F, feet into water at 45° C. Until the forty-fifth minute the arms and hands were in similar positions. After that the right hand was held in a hemiplegic posture.

FIG. 6.—McK., paraplegia. A, legs into water at 44° C.; B, legs into water at 13° C.

These experiments demonstrate that, in the presence of lesions of the cerebral hemispheres, irrespective of site, in response to changes in blood temperature, the rise and fall of temperature of the digits of the two hands, or of the two feet, are synchronous and of similar rate. The only exceptions are in those cases with marked spasticity of the arm when the temperature of the fingers of the spastic arm falls irregularly.

The following experiment was undertaken to investigate this later phenomenon. As the observations suggested that the spastic alteration in posture produced this irregularity of fall of temperature, it was decided that a healthy subject should imitate the abnormal posture and movements. Fig. 5 shows the result obtained. During the first period of cooling the arms were comfortably supported at the side as in the previous experiments. Following the subsequent warming, cooling was again induced, and during this period of cooling the right arm was voluntarily placed in the hemiplegic posture. In this instance cooling was less rapid and more irregular than in the left finger, which was kept supported at the side. The final temperature of the right finger was warmer than that of the left. This procedure was carried out in three normal individuals and gave results similar to those portrayed in fig. 5.

Discussion.

These observations have shown that, with certain minor differences, a rise and fall of skin temperature, similar to that seen in the normal, occurs in response to warming and cooling the body in patients suffering from hemiplegia. At the commencement of an experiment, the hemiplegic limb was sometimes colder or even warmer than the normal limb. This variation in the temperatures of corresponding skin areas on both sides of the body bore no demonstrable relationship to the site or age of the cerebral lesion. However, there may be an apparent delay in cooling of the hemiplegic limb. This may be taken as indicative of dysfunction of the sympathetic system. Before accepting such an hypothesis, it is well to take other factors into consideration.

It has been shown in these investigations that, during the period of cooling, the spastic hemiplegic limb tends to adduct at the shoulder and to flex at the wrist and finger-joints when the motor involvement is severe. As a result of this movement the fingers are brought closer together and nearer to the body. The closing of the fingers causes the approximation of comparatively warm surfaces, and prevents free cooling of these surfaces. In this way loss of heat, as indicated by a fall of temperature readings of the digits of the hemiplegic limb, may appear more slowly than in the opposite and healthy limb. Since a fall in skin temperature readings is indicative not only of a diminished blood flow, but also of the capacity of the limb to cool, it is essential to take into account the facilities for cooling. That the posture adopted in these cases during the cooling is of importance is evidenced by the experiment

in which a normal individual was subjected to cooling on two occasions. Here it was found that when the limbs were kept in a similar position, cooling was equally rapid on the two sides; but when one limb adopted the hemiplegic posture, cooling was less rapid on that side. This evidence strongly suggests that the posture, quite apart from the site of the lesion producing the posture, may account for the lack of synchronous cooling in the two limbs of a hemiplegic patient.

When describing the investigations undertaken, attention was drawn to the immediate cooling of already warm limbs on placing the indifferent limbs in warm water. As the water was of a temperature of 44° to 45° C. the sensation when immersing the limbs was at first unpleasant if not actually painful. It is, therefore, probable that this unpleasant sensation produced a vasoconstrictor response which showed itself by a cooling of the limb under investigation. Again, it was observed that in one or two subjects the immersion of the feet in cold water was followed by an immediate but short-lived cooling of the hands, with a subsequent warming and then a very marked cooling. The second cooling synchronized with the fall in rectal temperature. The immediate cooling was the result of constriction produced by the sensory stimulus of cold. This sensory stimulus was not sufficient to keep the vessels constricted, and they again dilated, only to constrict when the blood temperature, as indicated by the rectal temperature, began to fall. That such an explanation is likely to be true was demonstrated by a study of what occurs in the hands of a patient with a complete paraplegia when the lower limbs are used for immersion. In such a case cooling of the upper limbs did not occur till the rectal temperature had begun to fall (fig. 6). Thus it may be deduced that on immersing the limbs in cold water, two mechanisms play a part in bringing about the cooling of the upper limbs, first a sensory stimulus producing vasoconstriction, and secondly a vasoconstriction dependent upon the fall of temperature of the blood. A study of the results obtained from patients with hemiplegia shows clearly that both mechanisms act in the hemiplegic as in the normal limb.

The work described in this paper therefore favours the view that lesions of the cerebral hemispheres do not in any way alter the functional capacity of the blood-vessels of the hemiplegic limb to constrict in response to a sensory stimulus or to a fall in blood temperature; and secondly that, provided an adequate warming stimulus is presented, the blood-vessels of the hemiplegic limb will dilate as in the normal limb.

Summary and Conclusions.

Constriction and dilatation of blood-vessels in response to cooling and warming the body occur in the hemiplegic limb as in the normal limb.

Any delay in cooling the hemiplegic limb is the result of poor facilities for cooling owing to approximation of warm surfaces brought about by posture.

Vasodilatation and vasoconstriction of the vessels of the limbs in response to warming and cooling the body are not affected in degree or in time of onset by lesions of the cerebral hemispheres.

VASOMOTOR RESPONSES IN HEMIPLEGIC PATIENTS.[1]

BY G. STÜRUP (COPENHAGEN), B. BOLTON (LONDON), D. J. WILLIAMS (MANCHESTER), E. ARNOLD CARMICHAEL.

THE investigation of the responses of the sympathetic nervous system of man to various stimuli offers a method of analysis of the functional activity of this system in both health and disease. Of the different manifestations of sympathetic activity the vasomotor response provides a readily demonstrable and efficient indication of the state of the sympathetic system. Accordingly the vasomotor responses of normal subjects and of patients with diverse cerebral lesions have been investigated in some detail and an attempt has been made to record these changes accurately.

Skin temperature readings with thermocouples, as an indication of vasomotor activity, are subject to many uncontrollable variables. The posture of a limb, the local facilities for cooling, the condition of the skin, the activity of the sudomotor system, and the external temperature, each play a determining part in such temperature readings. It has been deemed advisable therefore to evolve a more exact method of registering vasomotor activity. A recognized method of undertaking such a study has been by plethysmography, and the literature on the subject is immense. In the earlier recorded investigations plethysmographic records of a whole limb were obtained by means of the Lehmann [2, 3], or a similar plethysmograph. As muscles are included within this apparatus it is impossible to deduce that the volume changes observed are entirely the result of change in blood volume and are not in part the result of changes in muscle state. Other investigators have constructed smaller plethysmographs; Weber [6] used an ear plethysmograph, and Lombard and Pillsbury [4] a finger plethysmograph. Unfortunately the latter apparatus was too delicate to use in a study of clinical material, and did not permit of more than one digit being examined at a given time. Moreover it was found that a single subject varied in the

[1] Work undertaken on behalf of the Medical Research Council at the Research Unit, National Hospital, Queen Square, London, while Dr. Stürup held a Rockefeller Foundation Fellowship and Dr. Williams a Halley-Stewart Research Fellowship.

character of the responses and it was therefore suggested that this variability depended upon the degree of "spasm" of the sympathetic nervous system. Cognizant of these difficulties and criticisms, an attempt has been made to evolve a satisfactory method of investigating the activity of the sympathetic vasomotor fibres of man in health and disease. It is the purpose of this paper to describe the method used, to record the results obtained in normal subjects and in patients with cerebral lesions, and to discuss their interpretation.

Method.

This has been described in detail in another paper [1]. Briefly, a digit was inserted in a glass container moulded to the shape of the finger or toe. Proximally the container was sealed round the finger with zinc oxide paste, and distally it was connected by means of pressure tubing to a thistle funnel covered with a rubber diaphragm, attached to which was a mirror. By means of a beam of light reflected from this mirror on to a moving strip of bromide paper, a continuous record of the changes of volume of a digit was obtained. By erecting a battery of diaphragm recorders, each connected to a different digit, it was possible to obtain synchronous records of changes of volume from several digits of one limb, or from individual digits of two or more limbs. As the rate of recording adopted was slow, the instrumental latent period of less than one-tenth of a second was negligible.

In order to ascertain if there was a quantitative difference in the bilateral response, a modification was introduced into the apparatus as originally described. The diaphragm recorders of two similar digits were repeatedly switched over in order that the possible errors caused by differences in the volume of air in the systems and in the tension of the tambours might be eradicated. In order to equalize the pressures in the system a water manometer was introduced, and the systems equilibrated before each set of stimulations was applied.

The subject was warmed by the immersion of one or two limbs in tanks of water at 44° to 45° C. in order to obtain a steady base-line from which to elicit responses. During this period of warming a continuous record of the changes of digital volume was obtained. It has been shown previously that this method of warming produces a widespread vasodilatation. During this state of dilatation a series of stimuli were given and records taken. The subject was then cooled down by placing the indifferent limbs in cold water at 10° to 12° C. Continuous records were obtained during this phase of the investigation. Skin

temperature readings were taken by thermocouples from the tips of the fingers and toes throughout the experiment, and alterations in rectal temperature were registered every quarter of a minute by a thermocouple placed 5 to 6 cm. above the anal sphincter. During the initial control period, and after the subject had been cooled down by immersion of the indifferent limbs in cold water, a similar series of stimuli was repeated.

The stimuli used to provoke vasomotor responses were various. These stimuli may be classified conveniently as extrinsic—cold, pressure, pain, noise; intrinsic—deep breathing, altered blood temperature, visceral pain; mental activity—calculation, word association. Other stimuli such as the threat of injury were also used. Each stimulus was known to be of sufficient intensity to produce a response in normal people. In every experiment a record of the phases of respiration was made by attaching a balloon to the chest. This was necessary in order to determine that the vasomotor response following the known stimulus was not the result of an alteration of respiratory rhythm. During the experiment the subject had his eyes closed and silence was demanded in the experimental room.

It is a pleasure to record our thanks to the members of the honorary staff of the National Hospital who kindly allowed us to carry out investigations upon patients under their care. To the post-graduate students who offered themselves as controls we also express our gratitude.

Results.

In a study of normal people it was found that if the subject were kept in a warm state by immersing one or more limbs in a tank of water at 45° C., the volume of a digit kept nearly constant (fig. 1). Two to three seconds following an extrinsic stimulus, such as a noise or pinch, there took place a diminution in the volume of the digits under investigation (fig. 1). This change of volume took place synchronously in all four limbs and reached its maximum in six to twelve seconds; the volume then returned over a period of a minute to its previous level.

Before investigating normal or abnormal cases it was established by the following series of experiments that the diminution in digital volume was in fact the result of a nervous vasoconstriction. In one patient, who had the right brachial plexus torn across eighteen months previously, and in whom there was wasting of the muscles of that limb and a complete anæsthesia, tests were carried out by taking observations

from the fingers of both hands. Following a pinch in a sensitive area no diminution in the volume of the digits of the limb with the ruptured brachial plexus took place; in the digits of the other limbs it did occur (fig. 2). This demonstrated that the diminution of digital volume was dependent upon the integrity of the peripheral nervous system.

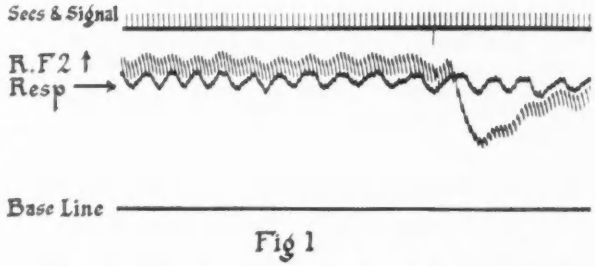

Fig 1

FIG. 1.—Normal. During a period of one minute there is no variation of volume of the finger apart from changes associated with normal respiration. At a signal a shout was given with resultant marked diminution in volume of the digit. The letters to the left indicate the digits. RF2 refers to 2nd right finger. In this and subsequent figures the RT or LT refers to right or left toe. The arrow following the identification mark of the digits points in the direction of an increase in volume. The downstroke in the respiratory tracing is the inspiratory phase. All records read from left to right.

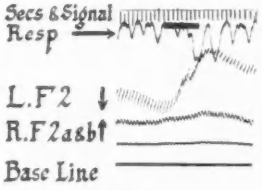

Fig 2

FIG. 2.—Lesion of right brachial plexus. Pinch left arm.

In two subjects, in whom a unilateral stellate ganglionectomy had been performed, no diminution in volume in the digits of the sympathectomized limb occurred following a stimulus. In another patient, who had had a unilateral lumbar ganglionectomy, there was no change in volume of the toes of that side following a pinch (fig. 3). These experiments established that the diminution in digital volume was dependent upon the integrity of the post-ganglionic sympathetic nerve-fibres. They also established that the recorded changes were not the result of movement of the digit within the container.

In a patient with a compression lesion of the cauda equina following an accident and in whom, at operation, the roots of the cauda equina were found to be grey, diminution in volume of the toes of both feet took place at the same time as that in the digits of the upper limb (fig. 4). In this patient the level of anæsthesia indicated that there

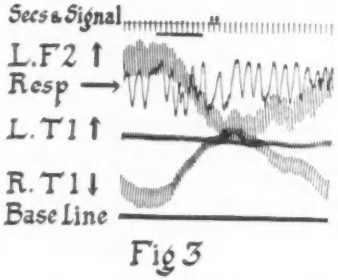

Fig 3

FIG. 3.—Left lumbar sympathetic ganglion excised. Pinch right arm.

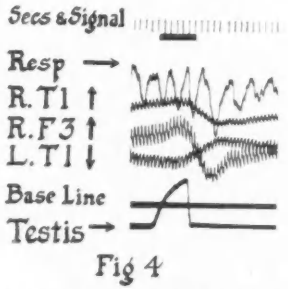

Fig 4

FIG. 4.—Lesion of cauda equina. Pressure of testis.

was no disturbance of the function of the lower dorsal and first lumbar roots by which the vasomotor preganglionic fibres to the leg leave the cord. But there appeared to be complete interruption of the lower lumbar and sacral anterior and posterior roots. It was therefore

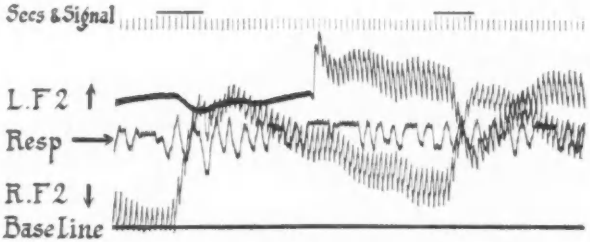

Fig 5

FIG. 5.—Normal. Circulation occluded in left arm during first period, then released. Pinch on right leg during and after occlusion of the circulation.

evident that the diminution in volume of the toes was independent of the motor and sensory nerves, and was accounted for by the integrity of the preganglionic fibres in the lower dorsal and first lumbar roots.

In three normal people the circulation in one limb was suddenly occluded by rapidly raising the pressure in two sphygmomanometer

cuffs, placed respectively on the forearm and upper arm, to over 200 mm. of mercury. Any stimulus sufficient to produce a diminution in volume of the digits with normal blood supply caused a synchronous change of the finger to which the circulation had been occluded (fig. 5). The diminution in volume of a digit was therefore not the result of alteration of heart output or of venous pressure.

These experiments showed that the alteration in volume of a digit, following an extrinsic stimulus, was dependent upon the integrity of the sympathetic nervous system. As the digits contain no muscle tissue this alteration in volume of a digit is therefore only explicable by an active vasoconstriction.

A study was made of twelve post-graduate students attending the hospital. None had evidence of vascular disease of the extremities. In the dilated state and irrespective of the nature of the stimulus a diminution in volume of the digits of the four limbs occurred synchronously after the commencement of any given stimulus. A painful stimulus, e.g. a pinch, or pin-prick, either single or multiple, caused a response wherever the site of stimulation. A sudden noise, such as was made by dropping a plank on the floor or shouting, was followed by a diminution in digital volume. Visceral pain, caused by pressure on the testicle, produced a similar response. The application of ice to any part of the exposed body was an adequate stimulus. Deep inspiration also resulted in a peripheral vasoconstriction [1].

If the subject were given some mental exercise, such as the multiplication of two figures, a diminution in volume of the digits took place in all four limbs. Again, word association resulted in a diminution in volume. The threat of injury, for example the threat of a blow on the face, was followed by a similar alteration in volume. All forms of stimuli resulted in synchronous vasoconstriction of the peripheral blood-vessels of the four limbs. The fall in finger volume did not immediately follow the stimulus. In every case there was a latent period which was never found to be less than one and a half seconds or more than three and a half seconds. It was the rule to find a sharp diminution in finger volume two and a half to three seconds after the stimulus was applied. When the stimulus was instantaneous and could be recorded with a fair degree of accuracy, such as a sudden loud noise or sharp pin-prick, the latent period was remarkably constant, being within two and a half to three seconds. With an intrinsic stimulus, such as a deep breath, it was impossible to ascertain the latent period, as it was not known at what time the stimulus, i.e. the degree of inspiration, had become

adequate. Even here, however, the change in finger volume occurred within four seconds of the commencement of deep inspiration.

During the course of these experiments with extrinsic stimuli several interesting observations were made. For instance, when forceps were laid on the skin without an actual pinch being made, a diminution in volume of the digits occurred. Upon holding the forceps there, and then giving a series of pinches at a time interval of thirty to forty-five seconds, diminution in volume occurred with the first pinch; but with succeeding pinches this gradually grew less, eventually ceasing to occur after the fourth or fifth stimulus. This was observed even though the last caused as much pain as the initial stimulus. If at this stage another stimulus, either of the same character or otherwise, were given at another site, widespread and well-marked diminution in digital volume

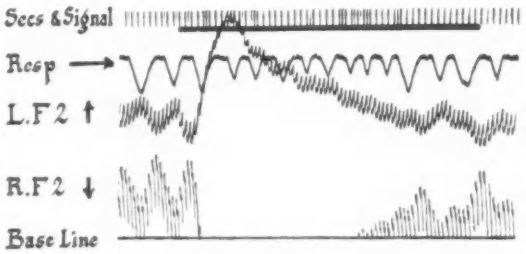

Fig 6

FIG. 6.—Normal. Pinch continued over a period of one minute. The arrows following L.F.2 and R.F.2 should point in the opposite direction.

resulted. When a pinch or multiple pin-pricks were continued for a period of a minute, during which time the subject continued to feel pain, a diminution in volume occurred at the commencement; gradually the volume returned to its original level (fig. 6).

Finally, it has been shown that the diminution in finger volume occurred irrespective of the respiratory rhythm. This was shown in two ways. First, the various stimuli were unassociated with an alteration in the respiratory rhythm (fig. 6). Secondly, with the breath held, a stimulus, such as a pinch, caused a diminution in volume of the digit, which returned to its preceding level during the period of holding of the breath (fig. 7).

With the subject in an initial state of vasoconstriction, further vasoconstriction as a result of a stimulus was difficult to demonstrate. Conversely, in the presence of vasoconstriction, vasodilatation would be

more evident. Although further vasoconstriction could still be produced, no vasodilatation ever occurred following a stimulus. During the period of increase in rectal temperature following the immersion of the indifferent limbs in warm water, an increase in digital volume was

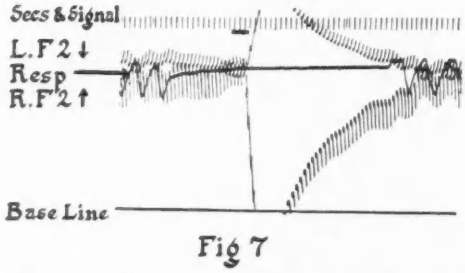

Fig 7

FIG. 7.—Normal. Pinch during a period of voluntary apnœa.

observed. This dilatation commenced only after the rectal temperature had begun to rise. Concurrently with the increase of finger volume there was an increase in the amplitude of the pulse wave. Fig. 8 shows clearly that this change is coincident with changes in the degree

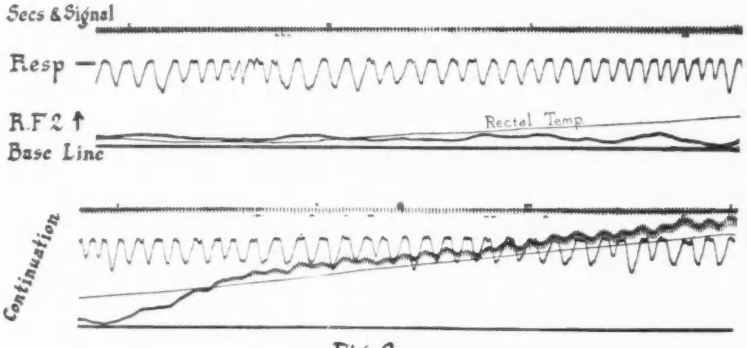

Fig 8

FIG. 8.—Normal. Period of warming up. Record of change in rectal temperature and in volume of right finger.

of vasodilatation. Irrespective of the limb used for immersion, the corresponding digits of the other limbs dilated synchronously in every case. When digital temperature readings were being recorded simultaneously, the dilatation preceded the increase in skin temperature.

On transferring the indifferent limbs to water at 10° to 12° C. there was an immediate constriction followed by a slow dilatation. This lasted for one to two minutes and was then replaced by a progressive vasoconstriction. This later vasoconstriction succeeded the fall in rectal temperature by a short time interval (fig. 9).

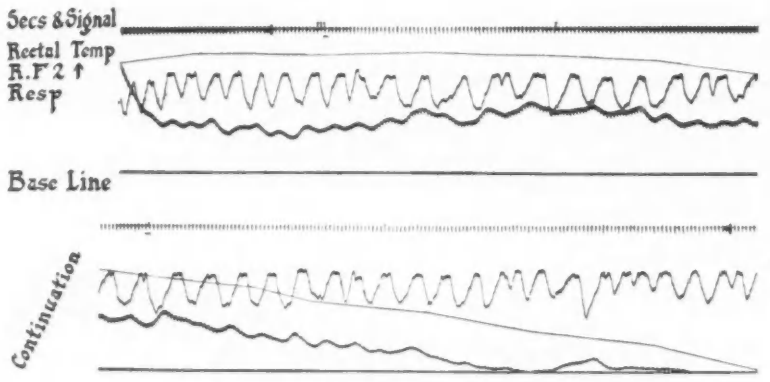

Fig 9

FIG. 9.—Normal. Record of commencement of cooling. At the beginning of the record the indifferent limbs were placed in cold water. The immediate diminution in volume is seen followed by an increase of volume of the digit. The curve of rectal temperature is plotted.

HEMIPLEGIA.

In all twenty-three patients with lesions of the cerebral hemispheres were examined. Of these, nine had symptoms of severe motor involvement, five of sensory involvement, four of both. Three had lesions of the frontal lobe, one a lesion of the occipital pole, and another of the temporal lobe. Fig. 10 illustrates the site of the lesion in these cases. Eleven patients were suffering from cerebral tumour, and ten from a vascular lesion. Cortical atrophy was the cause of the symptoms and signs in one patient and trauma in another. The age of the lesion varied from six days to twenty years. Several of those subjects suffering from cerebral tumour were examined before and after operation. Care was taken to exclude all patients who had gross evidence of vascular disease of the peripheral blood-vessels. Only patients in whom an accurate clinical localization of the lesion in the cerebrum was possible were included in the series, and the diagnosis of a few was subsequently confirmed at autopsy.

In all cases symmetrical synchronous records were obtained. In the majority corresponding fingers were used, in others corresponding toes. Records were taken from digits of three and even four limbs simultaneously in several cases. In the latter instance the subject was warmed by several hot-water bottles and extra blankets. Though not so efficient as the immersion method for giving a steady baseline, it was

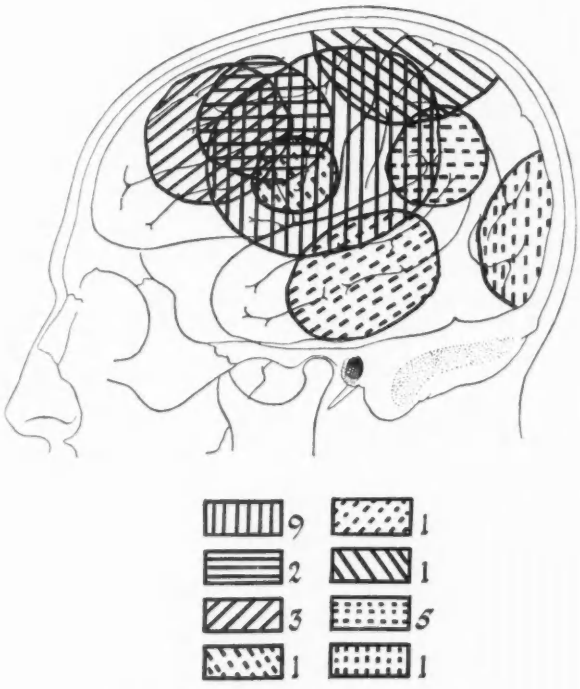

FIG. 10.—Chart of sites of cerebral lesions.

still possible to determine the presence or absence of diminution of digital volume following appropriate stimuli.

The results of these observations may be quite briefly given: for no matter where the site of the lesion in the hemisphere, or what the degree of dysfunction of motor, sensory, or of reflex activity, the results so obtained were identical with those from normal individuals. In those subjects with marked sensory disturbance on the one side, extrinsic stimuli applied to the affected side caused a similar response to that

produced by stimulating the normal side. Further, in subjects with severe motor involvement or in those suffering from a lesion of the frontal lobe, the diminution in volume of the digits of both upper limbs was alike in response to the stimuli. Mental activity, fright and visceral pain also produced symmetrically good responses. The outcome of these investigations was to demonstrate that with lesions of the

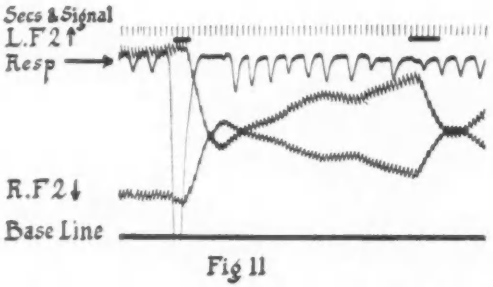

FIG. 11.—Left frontal lobectomy. Deep breath and pinch of right arm.

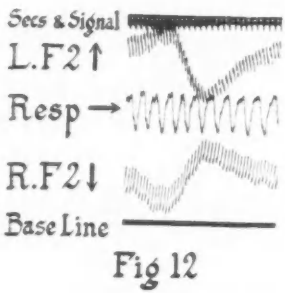

FIG. 12.—Left motor cortex destroyed. Shout.

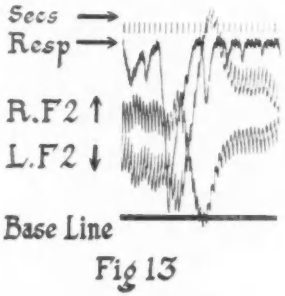

FIG. 13.—Left parietal lobe lesion. Deep breath.

cerebral hemisphere, no matter the site or the resultant severity of dysfunction, vasoconstriction could be produced in the fingers or toes of the two sides with ease and regularity equal to that in normal individuals (figs. 11, 12, 13).

In twenty patients tests were carried out with the subject in a cool state—namely one in which vasoconstriction of the peripheral vessels was present. The presence of vasoconstriction was assumed by the temperature of the fingers, measured by thermocouples, and also by

plethysmographic records which illustrated the relative smallness of the pulse-wave in the records. During this state of vasoconstriction they were subjected to all the stimuli which have been described. A close analysis of the records failed to demonstrate any response which could be interpreted as indicative of dilatation.

Twenty subjects with a lesion of one hemisphere, who were in a cold state, were warmed up by placing either the legs or arms in tanks of water at 44° to 45° C. During this period continuous records were taken from the digits of the other limbs. After an irregular period of time, varying from three to fifteen minutes following immersion, and only after the rectal temperature had begun to rise, an increase of volume of the digits occurred, associated with an increase in the amplitude of the pulse-waves. The records showed that the increase in volume and pulse-wave amplitude occurred synchronously in the digits of both arms or legs. No priority or delay was ever seen in the dilatation of the hemiplegic limb.

Lastly, after taking records while in a fully dilated state, the subjects were cooled rapidly by transferring the indifferent limbs from tanks of warm water to tanks of water at 12° to 15° C. Immediately upon placing the limbs in the cold water a diminution in volume of the digits under observation took place; this was followed by a slow dilatation but not to the level attained before cold immersion. This period of slow dilatation was followed one to two minutes later by a renewed diminution in volume and lessening of the amplitude of pulse-wave. Synchronous rectal temperature readings showed that the secondary diminution in volume occurred at the same time as the rectal temperature ceased to rise and began to fall. The records obtained from patients suffering from cerebral lesions demonstrated that, on immersion of the other limbs in cold water, the vessels of the digits of both the hemiplegic and normal limb constricted, then dilated and finally constricted synchronously. No record was obtained which showed any delay in the healthy or hemiplegic limb.

Discussion.

In these experiments care was taken to exclude movement of the recording digits and to ensure complete absence of congestion of the digit by pressure of the proximal end of the plethysmograph. These variables being absent, change in the volume of the finger could only be brought about by change in heart output, venous pressure, or by active alterations in the state of the vascular network of the digit. After

completely occluding the circulation of an arm by a sphygmomanometer pressure of 200 mm. Hg it has been shown that a diminution occurred in the volume of the finger after stimulation. The curve of this diminution of volume was of the same type and had the same time relations as those changes produced in the presence of a free circulation. It can therefore be affirmed that these changes in the digital volume are directly produced by changes in the vascular bed—that is, by vasoconstriction. Experiments on patients with lesions in different sections of the peripheral pathways have been described. It has been shown that vasoconstriction in response to intrinsic and extrinsic stimuli is independent of the integrity of the anterior and posterior roots of the recording limb, but that it is dependent on the continuity of both the pre- and post-ganglionic sympathetic nerve-fibres. It is therefore a mechanism whose efferent pathway is a sympathetic nerve-fibre. In the patient with the cauda equina lesion, although stimulation of the skin above the level of anæsthesia caused a vasoconstriction in the affected limbs, stimulation of the anæsthetic limbs did not produce vasoconstriction. Again in the patient with the brachial plexus injury, stimulation of the affected limb caused no constriction in other limbs. In the sympathectomized patient however, stimulation of the periphery of the sympathectomized limb, although causing no change in volume of the sympathectomized fingers, resulted in vasoconstriction in the normal digits of the other limbs. This evidence points to the necessity of an intact sensory pathway when stimuli such as pain, cold, pressure were used.

The latent period of the vasoconstrictor response has been described above. The intensity and the type of stimulus applied did not appear to bear any relation to the latent period observed, although they did affect the degree of vasoconstriction. The constriction was synchronous in all the digits examined.

It has been said that the subjects were examined in dilated and in constricted states. In the course of the experiments stimuli of all the types described above have been applied repeatedly in different ways, but when a response has been elicited it has invariably been a vasoconstriction.

The regional distribution of the lesions has been described. Reference to fig. 10 shows that several regions are represented by more than one patient and it is our belief that the extent of damage illustrated is not excessive. It is therefore unlikely that any part of the motor or sensory areas can have escaped damage in this series. The age of

these lesions and the degree of motor and sensory involvement has also been ascertained. In the presence of such damage, with resulting dysfunction, no difference from the normal in the vasomotor responses were found in these subjects. Both the time relationships and degree of vasoconstriction were unchanged. As has been pointed out above, the vasodilatation and vasoconstriction in response to alterations in blood temperature were identical in the normal and hemiplegic side.

In a paper [5] dealing with skin temperature readings it has been shown that in hemiplegia no consistent difference in the initial skin temperature could be found between the two sides. The alteration in skin temperatures in response to changes in blood temperature was similar. It was shown further that the skin temperature of the hemiplegic side might be influenced by posture and bore no relation to the age of the lesion. These conclusions are confirmed by the results of the present paper. It can be affirmed that these investigations provide evidence that, in the presence of lesions of the cerebral hemisphere, the vasomotor control of the limbs is unaffected.

Conclusion.

No abnormality of the vasomotor responses in the limbs has been found in the presence of lesions of the human cerebral hemisphere.

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MYOGRAPHIC AND ELECTROMYOGRAPHIC STUDIES OF MYASTHENIA GRAVIS.[1]

BY DONALD B. LINDSLEY.[2]

MYASTHENIA gravis is a condition characterized by marked muscular weakness and excessive fatiguability, particularly in the muscles innervated by the cranial nerves. In such cases chewing, swallowing, keeping the eyes open, holding the head erect and speaking are difficult. The weakness and fatiguability often extend to the muscles of the limbs and trunk so that the patient not only experiences difficulty in breathing, but also in maintaining his general welfare.

Little is known about the cause or exact nature of this disorder. No consistent and definite pathology of either the peripheral or central nervous system has been demonstrated. Minor anatomical changes occasionally found in the muscles are probably not of primary significance. During the past few years, reports by Boothby [1], Remen [2] and others on the beneficial results of glycine treatment have pointed to a disturbance of creatine and creatinine metabolism in myasthenia gravis. Nevin [3], however, in a recent study of the phosphorus-holding compounds of muscle in myasthenia gravis, found them normal and concluded that there is no abnormality in the intrinsic chemical mechanism of muscular contraction in this disorder. He believes that alterations in creatine metabolism are secondary effects of the disease. Simon [4] has recently reported marked improvement in two cases of myasthenia gravis following treatment with anterior pituitary extract.

The view that the transmission of excitation is somehow impaired in the region of the "myoneural junction" has arisen partly because of the exclusion of other factors, and partly because of Edgeworth's [5, 6] discovery that ephedrine is of value in the treatment of this disorder. Recent success in temporarily relieving myasthenic symptoms with physostigmine [7, 8] and the synthetic drug, Prostigmin [9, 10, 11, 12, 13, 14], has materially strengthened this view.

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[2] National Research Council Fellow.

The present study is a part of a general programme of investigation of neuro-muscular disorders by electromyographic methods, and makes use of a technique for studying the electrical potentials of single motor units (groups of muscle fibres innervated by single neurones). Adrian and Bronk [15] first demonstrated that electrical potentials from the smallest functional unit of the neuro-muscular system, a group of muscle fibres and its controlling motor neurone, could be obtained from an intact human muscle by means of coaxial needle electrodes inserted into the muscle. Adrian [16], Smith [17] and Lindsley [18] have since described in some detail the characteristics of the responses of single motor units in normal human muscles.

Apparatus and Method.

The apparatus consisted of a six-stage transformer-coupled amplifier,[1] which drove either a loud speaker or a Du Bois oscillograph. The electrodes were of the coaxial type, consisting of a hollow steel hypodermic needle which served as a ground lead and a fine insulated wire cemented into its lumen which served as a grid lead.

When myographic records were made in response to electrical stimulation of the ulnar nerve, an isometric myograph was used. The arm of the subject was tightly bound, volar side down, to a splint-board in such a manner that the entire forearm and hand were immobile with the exception of the fifth finger, which extended over the edge of the board. The finger was enclosed in a snug aluminium thimble so that flexion could occur only at the metacarpo-phalangeal joint. The thimble was attached to the myograph lever and was flanked on each side by two vertical uprights which prevented the finger from moving sideways when it flexed.

The stimulating electrodes consisted of brass plates covered with canton flannel soaked in saturated NaCl solution. The small electrode (1 by 4 cm.) was bent to fit the curvature of the arm and was securely attached just proximal to the internal condyle of the elbow-joint and slightly medialward where it was found to stimulate the ulnar nerve most effectively. The large electrode (5 by 5 cm.) was attached to the calf of the opposite leg. Maximal stimulating shocks were provided by discharging through the subject a 1 μF condenser charged to 16 volts. A rotary interrupter afforded various stimulating frequencies.

Description of Cases.

Case 1.—A male, aged 18, was admitted to the neurological service of the Massachusetts General Hospital in June, 1932. Fatigue and weakness had been noticed for ten months, although previously he had been as strong and

[1] An amplifier of this type distorts the wave form of the action potential appreciably, but is perfectly adequate for studying the responses of single motor units so far as rhythm and amplitude are concerned.

active as other boys. He could walk only about 200 yards; could climb but one flight of stairs; fell often when he walked and could not get up alone; experienced difficulty lifting extremities; had trouble elevating self from a prone or supine position; felt drowsy and lethargic at times; experienced difficulty in chewing and swallowing.

Physical examination revealed generalized muscular weakness without apparent atrophy; bilateral ptosis, more marked on the right; right facial weakness; external ophthalmoplegia; difficulty swallowing a thick barium meal; chest examination (thymus) normal; typical Jolly reaction in all muscles on faradic stimulation.

He improved slightly with ephedrine, and continued taking it in doses of from 1 to 3 gr. daily for a year. When ephedrine was stopped for a week he became worse. There were partial remissions and exacerbations, but when seen in the out-patient department in September, 1933, his condition was the same as on first admission. In October, 1933, he was again admitted to the hospital. There was still marked ptosis on the right, but his facial expression was slightly improved. Respiration was weak and shallow. He fatigued quickly upon alternate supination and pronation of hands. The extensors of the leg and the sterno-cleido-mastoids were especially weak. He reported that the hand, arm and jaw muscles became tired soon after a meal was begun.

He has continued to take ephedrine sulphate until the present time with some beneficial effect. In December, 1934, he was given 30 grm. of glycine daily with ephedrine. He continued this for one month without greater benefit than when ephedrine was taken alone. At present he is not able to climb more than one flight of stairs or walk but a short distance. He cannot raise his arms to the level of his shoulders. Grip on a hand dynamometer is between 5 and 8 kg. An intravenous injection of benzedrine sulphate (10 mgm. in 30 c.c.) had no beneficial effect. Prostigmin, on each of several occasions, has relieved practically all symptoms for a few hours.

Case 2.—Male, aged 64, admitted to neurological ward of Massachusetts General Hospital in November, 1934. The chief complaints were: difficulty in speaking and swallowing, dating from eighteen months, but with remissions during past sixteen months; regurgitation of liquids and an inability to bite and chew solid foods; difficulty in spitting and in holding the head erect; choking sensations and inability to breathe at times. There was no difficulty in writing and no marked weakness of limb or trunk muscles. Ephedrine was given from November 9 to 20 with improvement, the patient feeling considerably stronger. Ephedrine was omitted for one day with immediate return of difficulties in speech and swallowing. Ephedrine 1·5 gr. and glycine 30 grm. daily, have been taken during the past five months with marked improvement of strength in face, neck and jaw muscles. However, the patient still has some difficulty swallowing rapidly and in speaking clearly. Prostigmin completely relieves him of these difficulties for approximately three hours.

Case 3.—A female, aged 13, was admitted to the neurological ward of the Massachusetts General Hospital in March, 1934. Five months before entry ptosis of the lids appeared and diplopia shortly afterwards. She could walk and run, but tired quicker than other children; was unable to chew food satisfactorily; had almost complete ophthalmoplegia; was barely able to show her teeth and unable to close her eyes. The jaw muscles were weak, but the tongue protruded fairly well. The hand grasps were slightly weak and the biceps and triceps muscles were weaker than normal. No marked weakness of lower limb muscles was demonstrable, but she complained of weakness in her legs after walking or climbing stairs. The pupils were equal and reacted well to light; the fundi were unchanged; tendon reflexes were normal; there was a fine tremor of the extended fingers and slight ataxia: a typical Jolly reaction was observed in arm and hand muscles on faradic stimulation; chest X-rays were negative. Several trials with ephedrine, 1 to 5 gr. daily, have proved to be of little benefit. Chocolate is thought by the patient to have a beneficial effect. Prostigmin gave complete relief for a few hours.

Case 4.—A female, aged 15, first noticed difficulty in speaking five months before admission to the Massachusetts General Hospital in March, 1935. When speech was continued for a few minutes it became thick and unclear. One month later she noticed difficulty in swallowing, especially at the end of a meal. The difficulties in speech and swallowing have gradually grown worse. On admission she was able to read aloud only three or four minutes before becoming inarticulate. There was drooping of the eyelids and weakness of the facial muscles of expression. Regurgitation of liquids through the nose occurred at times. The muscles of the limbs were not weak but often felt tired. Her condition was always worse at the end of the day. Prostigmin temporarily improved her speech and facial expression very markedly.

Myographic and Electromyographic Examinations.

When coaxial needle electrodes were inserted in the affected muscles of the four patients and responses of single motor units recorded during voluntary contractions, obvious differences were noted between the records and those obtained from the muscles of normal human subjects. The same regular rhythm was apparent, but there were wide variations in the amplitude of the single motor unit responses, which are not characteristic of the records obtained from normal human subjects (fig. 1). With the early onset of fatigue in myasthenia gravis, even during weak contractions, the amplitude of the repetitive responses of a single motor unit becomes more variable and the unit often completely fails to respond, without in any way altering the fundamental rhythm.

Fig. 2 shows typical examples from a series of records obtained at ten second intervals from the rectus femoris muscle of Case 1, during

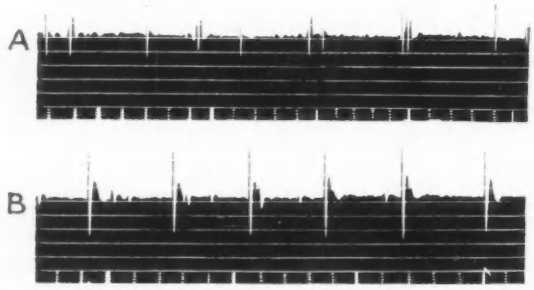

FIG. 1.—Typical single motor unit responses from normal human muscles during voluntary contraction, showing the regular rhythm and uniform amplitude. (A) from rectus femoris muscle showing two units at slightly different frequencies; (B) from tibialis anticus muscle. Time intervals at bottom of each record equal 0·023 sec.

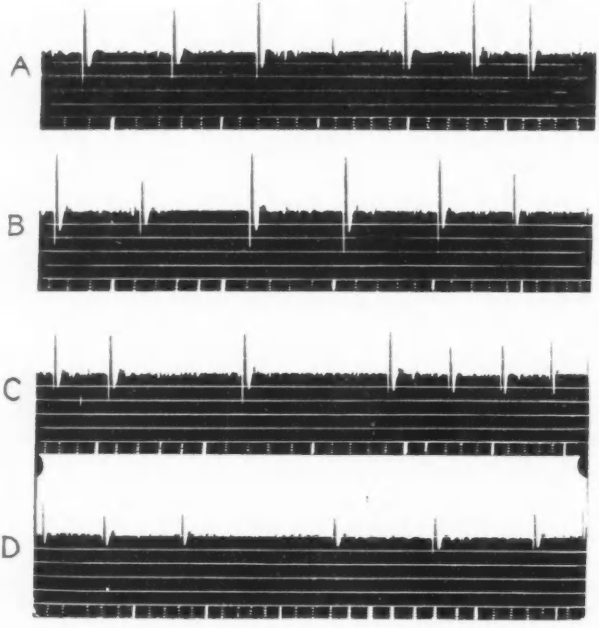

FIG. 2.—Responses of a single motor unit from the rectus femoris muscle of a myasthenia gravis patient (Case 1) during a weak contraction, showing the fluctuations of amplitude characteristic of this disorder. (A) at the start of the contraction; (B) after 40 seconds; (C) after 80 seconds; (D) after 170 seconds. Time intervals equal 0·023 sec.

a voluntary contraction (extension) maintained as long as possible. The muscles of this patient were all involved in the myasthenic condition, but the thigh muscles were particularly affected, so that he was usually able to maintain a contraction of this type only about two or three minutes before complete fatigue. The patient was sitting comfortably in a chair with one leg hanging over a padded cross-bar, the foot just clearing the floor. A rigid obstruction immediately in front of the ankle prevented actual shortening of the muscle or movement of the leg when voluntary extension was attempted. The needle electrodes were usually inserted to a depth of from 1 to 4 cm. and held securely in place by means of an adjustable holder attached to the leg.

Record (A) of this series, taken shortly after the start of the contraction, shows the rhythmic responses of a single motor unit. The first three responses are of uniform amplitude and do not differ from the normal. The fourth response and also the eighth are greatly diminished in amplitude. Record (B), obtained thirty seconds after the start of the contraction, shows further irregularity in amplitude, the second and sixth responses being diminished in size and the seventh being just barely visible. Record (C), taken after 140 seconds, shows some irregularity and a general decrease in amplitude of all responses with the complete absence of the third and fifth responses, although the rhythm is maintained as if they had occurred. The final record (D), obtained 170 seconds after the contraction began and just prior to complete fatigue, shows additional fluctuations of the responses and a general diminution of amplitude with absence of the fourth response.

Case 2, in whom the myasthenia was limited to the muscles of bulbar innervation, showed marked weakness and fatigability of the muscles of mastication, swallowing and speech. The neck muscles were also weak. With the needle electrodes inserted in the left sterno-cleido-mastoid muscle while the head was voluntarily turned to the right against restraint, records were obtained which show the same characteristic fluctuations in amplitude as in Case 1. Records were also obtained from the flexor digitorum sublimis muscle of the forearm during maintained flexion of the middle finger. This muscle was not noticeably involved in the weakness, and it is of interest that the single motor unit responses showed but very slight variations in amplitude, so little, in fact, that it was difficult to distinguish the records from those of a normal subject.

The same irregularity of amplitude of single motor unit responses has been observed in records obtained from the biceps and tibialis

anticus muscles of Cases 3 and 4. In a record from the biceps muscle of Case 3, for example, during a weak voluntary contraction, the amplitude varied considerably twenty seconds after the start of the contraction and also during the next sixty seconds. At the end of 90 seconds the unit was responding only occasionally, and many responses were completely absent. At this point the patient was so fatigued that she could maintain the contraction no longer. Although in Cases 3 and 4 the greatest weakness was observed in the less accessible muscles of the face and neck, it is of interest that the records of single motor unit activity in other muscles of the body show the characteristic fluctuations of amplitude.

The rhythm of the single motor unit responses in all cases was as regular as that of normal human muscles and there were no variations in rhythm which correlate with the fluctuations of amplitude. Even where one or two responses were completely absent the regular rhythm of the unit was maintained and subsequent responses appeared "on time."

The effect of prostigmin.—Several recent reports in the literature have indicated the prompt and striking effect of intramuscular injections of prostigmin in temporarily relieving the symptoms of myasthenia gravis. Prostigmin has been tried in all four cases here reported and found to have the same remarkable effect described by others. The usual doses of prostigmin (3 to 5 c.c.) with atropine $\frac{1}{100}$ gr. have been given intramuscularly. The maximum effect is reached within thirty minutes and usually continues for about two to three hours, depending, of course, upon the severity of the case, the dosage given, and the amount of activity indulged in by the patient. The effect has usually passed off completely in six hours.

Five minutes following an injection (5 c.c.), Case 1 reported a feeling of tenseness in the facial muscles, particularly around the eyes. In ten minutes the ptosis of both lids disappeared and a remarkable change in facial expression was apparent. Twenty minutes after the injection the patient was able to raise his arms to the level of his shoulders or above his head, jump off the floor, arise easily from a prone or supine position and perform several acrobatic feats hitherto impossible. After thirty minutes his grip had increased from 6 kg. with the right and 8 kg. with the left to 31 kg. and 33 kg. respectively. Sitting in a chair with his leg over a cross-bar before the prostigmin was given, he was able to extend the right leg to a horizontal level only twenty times and the left twenty-five times, whereas thirty minutes after the injection he extended each leg sixty times without sign of fatigue.

Although Case 2 improved remarkably on ephedrine and glycine, speech and swallowing were still affected and there was weakness of facial and neck muscles. Following an injection of 3 c.c. of prostigmin with atropine $\frac{1}{100}$ grm., the eyes opened wide and facial expression improved. Before the injection he was able to drink water only by resting between swallows, whereas twenty minutes after the injection he could drink a glass of water rapidly and without hesitation. Speech returned to normal. The strength of grip which was thought to be normal before the injection remained the same. The duration of the relief was about four hours.

Case 3, before an injection of prostigmin, lacked facial expression and all the muscles of the face, neck and jaw were weak. There was almost complete ophthalmoplegia and diplopia. Speech was weak and indistinct. Following the administration of 3 c.c. of prostigmin with atropine $\frac{1}{100}$ gr., these symptoms were almost entirely relieved for a period of three hours.

Case 4, following a similar injection, became alert and wide-awake. Her eyes opened wide and facial expression improved greatly. She was able to read aloud for fifteen to twenty minutes without any difficulty, whereas before the injection she could read aloud only three or four minutes before speech became indistinct and impossible. She was able to hold her eyelids tightly closed and strongly resist attempts to open them, which she had not been able to do previously. Hand dynamometer readings increased from 22 kg. on the right and 20 kg. on the left before the injection to 35 kg. on the right and 32 kg. on the left, forty minutes afterwards.

Electromyographic records obtained immediately before the injection of prostigmin and again thirty minutes afterwards show that the single motor unit responses, which were irregular and often absent before, were consistently present and of quite uniform amplitude after prostigmin. These remarkable changes are shown in some typical records presented in fig. 3. In every case, responses of several different motor units obtained before prostigmin showed the typical irregularity of amplitude, whereas thirty minutes after the injection responses of single motor units in various parts of the same muscle showed consistent uniformity of response.

Pritchard [19] reported characteristic myographic tracings from the little finger of myasthenia gravis patients when the ulnar nerve was stimulated at various frequencies. He found, in such cases, that at high frequencies (80 to 500 per second) the myograph curve, unlike

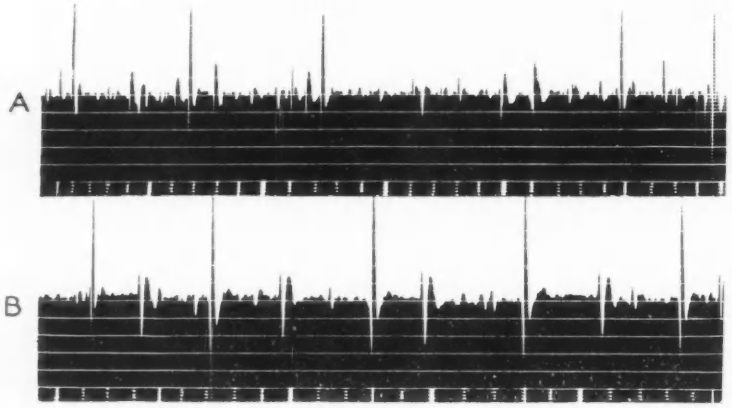

FIG. 3.—Records from the rectus femoris muscle of a myasthenia gravis patient before and after prostigmin. (A) typical single motor unit responses before, showing the irregularity of the amplitude and complete absence of the fourth response; (B) typical record 30 minutes after prostigmin, showing two units of regular rhythm and uniform amplitude. Time intervals equal 0·023 sec.

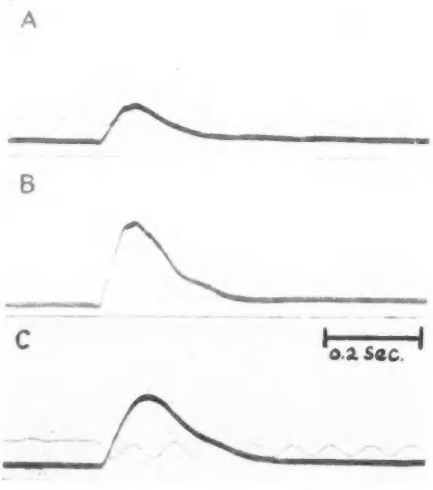

FIG. 4.—Myograph curves of flexion of fifth finger in response to single shocks through the ulnar nerve. (A) myasthenia gravis patient before prostigmin; (B) 30 minutes after prostigmin; (C) normal subject. Ignore faint wavy line.

that of a normal subject, failed to maintain its initial level and the tension gradually diminished with continued stimulation. The higher the stimulating frequency, the greater the rate of diminution. This he interpreted as an example of Wedensky inhibition. In later communications [10, 11] he has reported the effect of prostigmin in restoring the myograms of myasthenia gravis patients to normal.

Using a very similar technique, we have obtained myographic records from Case 1 and a normal control. Our results agree fundamentally, although not in all details, with those of Pritchard. His report [19], for example, indicated that for single shocks or low frequencies of stimulation (40 per second), the myograms in myasthenia gravis were essentially normal, whereas our records (fig. 4) show that

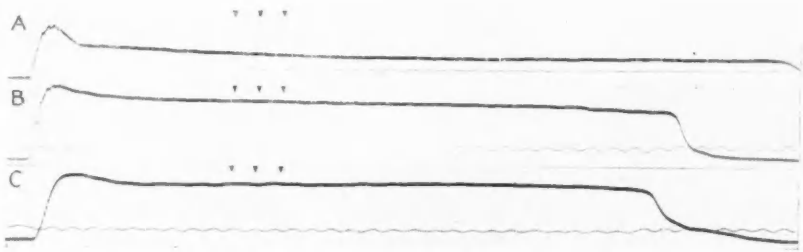

FIG. 5.—Myograph curves of flexion of fifth finger in response to repetitive stimulation (80 per second) through ulnar nerve for approximately 3 seconds. (A) myasthenia gravis patient before prostigmin; (B) 30 minutes after prostigmin; (C) normal subject. Time intervals at top of record equal 0·10 sec. Ignore faint wavy line.

the response to single maximal shocks before prostigmin (A), was much smaller than the response thirty minutes afterwards (B), or than that of the normal subject (C). It is obvious that prostigmin substantially increased the amount of tension developed in response to a single shock. Likewise, with frequencies of stimulation as low as 10 per second, the level of the myograph curve was in every case substantially increased by prostigmin. With higher frequencies of stimulation (80 to 480 per second) we have found that the myograph curve of the myasthenic patient resembles those described by Pritchard. Fig. 5 shows records obtained from the myasthenic patient before and after prostigmin and from the normal subject, using a stimulating frequency of 80 per second. Before prostigmin was given the myograph curve (A) rose to an initial maximum which was not maintained and although stimulation was continued for approximately three seconds, the curve gradually fell to

a considerably lower level. On the other hand, thirty minutes after the injection of prostigmin the myograph curve (B) reached a much higher initial level and maintained it fairly well throughout the course of stimulation. The curve decreases slightly, but very closely resembles the curve (C) from the normal subject. The myograph curve of the normal subject maintains a level plateau during continued stimulation at this frequency. We have found, however, that at higher frequencies of stimulation (330 to 480 per second) the normal myograph curve fails to maintain its initial height and falls to a slightly lower level, which it maintains during the course of continued stimulation. The curve of the myasthenia gravis patient, in response to these higher frequencies, reaches an initial maximum which is less than the normal and rapidly descends to its base-level. Following prostigmin, however, the curve is similar to that of the normal subject.

Discussion.

The fact that the motor unit in myasthenia gravis maintains its regular rhythm, whether its electrical response is a fraction of its original amplitude or entirely absent, indicates that the motor neurone is functioning normally and conveying a regular succession of impulses to the muscle. Therefore failure of response must be due to a blocking of the transmission of excitation at the "myoneural junction", or to a prolonged recovery period of the muscle. The latter could hardly be the case, since in fig. 1 the frequency of the response is 10 to 13 per second, which would allow from 75 to 100 milliseconds between responses for recovery. In addition, a full-sized response often occurs immediately following one of diminished amplitude without change in the duration of the interval between responses.

The characteristic irregularities of amplitude of the action potentials of the single motor unit and the associated weakness and fatiguability of the muscles are therefore due to the failure of the nerve impulse to excite some or all of the muscle fibres controlled by the motor neurone. If the neurone sends branches to one hundred or more muscle fibres which compose a unit [20, 21], irregularity in amplitude would seem to result from a blocking of excitation to a variable number of the muscle fibres supplied by the neurone. This would also result in a similar variation of tension.

Following the administration of prostigmin (an analogue of eserine), the action potentials are restored to a consistently uniform height along

with the return of normal strength. Likewise, the myograph curves of tension in response to single and repetitive shocks through the ulnar nerve show a substantial increase after prostigmin. Since it has been shown that eserine prevents the inactivation of acetylcholine by blood esterase [22, 23, 24], the above results strongly suggest that acetylcholine or a related choline ester plays an important part in the transmission of excitation at motor nerve endings in skeletal muscle.

In view of the many investigations (*see* Dale [25, 26]) which are rapidly supplying evidence of chemical mediation of excitation both at ganglionic synapses and at sympathetic and parasympathetic nerve endings on smooth muscles and glands, it is not surprising that this and other studies [27] point to a similar mode of excitation at motor nerve endings in voluntary muscle.

Summary.

(1) Action potentials from single motor units of the affected muscles of four myasthenia gravis patients showed abnormally marked fluctuations in amplitude.

(2) The persistence of a regular rhythm of the single motor unit responses, although wide variations in amplitude occurred, indicates that the nerve is functioning normally and sending a regular succession of impulses to the muscle.

(3) Myograph curves of flexion of the fifth finger in response to stimulation of the ulnar nerve with single and repetitive shocks showed diminished initial tension which rapidly decreased with continued stimulation.

(4) Following intramuscular injection of prostigmin the symptoms of weakness and fatiguability temporarily disappeared, the action potentials were restored to a uniform height and the myograph curves became practically normal.

(5) These results are interpreted as strongly suggesting that acetylcholine or a related substance is liberated at motor nerve endings and takes part in the transmission of nerve impulses to voluntary muscles.

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THE PERIPHERAL NERVES IN CASES OF SUBACUTE COMBINED DEGENERATION OF THE CORD.

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IT has been suggested by many writers that some of the symptoms of subacute combined degeneration might be due to lesions in the peripheral nerves. But microscopical proof of the presence of such lesions has never been conclusive, although degenerative changes have occasionally been observed. Thus Russell, Batten and Collier found "very considerable degeneration both by the Marchi and Weigert-Pal method" in the nerve to the vastus internus muscle in their Case 1, and "some degeneration in the left sciatic and left anterior crural nerves, and more in the left than in the right phrenic nerve" in their Case 2. Von Noorden found considerable degeneration of the tibial nerves though not of the crural nerve in one case, and Mathieu reported a case in which the myelin sheaths of the sciatic nerve were beaded. Hamilton and Nixon made a careful study of the anterior tibial nerves in their cases by the Weigert, Marchi and Bielschowsky methods. They found definite degeneration by the Marchi method in six, and by the Weigert-Pal method in four of their cases. On the other hand, many authors (Lichtheim, Minnich, Nonne, Burr, Boedeker and Juliusberger) have reported that the peripheral nerves in cases studied by them were normal. In view of such conflicting observations it was considered worth while to re-examine this question.

METHOD AND RESULTS.

Peripheral nerves were obtained from a series of cases of subacute combined degeneration. In the early cases of this series the nerves were stained by Weigert-Pal, Marchi and Gros-Bielschowsky methods. These methods, though indicating an abnormality of the nerves in their peripheral branches were found to be in some ways unsatisfactory. The Weigert-Pal method failed to stain completely the finest myelinated fibres, which failure might result in a misleading appearance in a nerve containing a large proportion of small myelinated fibres. The Marchi

(Busch) method was unreliable for two reasons. First, it is well known that any stretching or handling of a small nerve may give rise to appearances in Marchi preparations which are almost indistinguishable from those of early degeneration. Secondly, it was considered unsatisfactory to use in chronic cases a method which only demonstrated progressive changes. The Gros-Bielschowsky method gave excellent staining of nerve fibres in celloidin sections. No definite lesions could be seen in nerves examined by this technique, even when the number of myelin sheaths appeared to be greatly reduced in sections of the same nerve stained by the Weigert-Pal method.

It was therefore decided to stain the myelin sheaths by placing the nerves in 1 per cent. osmic acid for twenty-four to thirty-six hours immediately after they were removed from the body. As it was considered desirable that an examination should be made of nerves obtained from living patients, as well as from post-mortem material, attention was confined to the terminal portion of the internal branch of the anterior tibial nerve which lies between the 1st and 2nd metatarsals. This nerve was dissected out with care and a portion removed under local anæsthesia from patients without causing any discomfort or disability. A piece about 2 to 3 cm. long was taken, and, after treatment with osmic acid, the central part was cut in paraffin, both in the longitudinal and transverse planes. The material examined in this way was taken from four cases of subacute combined degeneration of the cord (one at autopsy, the rest during life), two cases of alcoholic neuritis (one during life), and one of acute infective polyneuritis. Control material was taken from patients with cerebral tumour and cerebral arteriosclerosis dying at various ages. The diagnosis of subacute combined degeneration in the living patients was made only after adequate blood investigation had been carried out, such as blood-count, hæmoglobin content and a Price-Jones curve. When a megalocytic anæmia was found the reticulocyte response to liver therapy was tested. There was also in the three living patients an absence of free HCl after an alcohol test meal during which histamin was given subcutaneously.

In order to determine if demyelination of a nerve bundle had taken place, a count of the number of myelin sheaths per square millimetre of nerve in transverse section was made. This was done without difficulty in photomicrographs of nerve bundles enlarged to 800 or 1,000 diameters. A survey showed that whereas in five normals the nerve bundles from the nerve chosen contained from 5,000 to 10,000 myelin sheaths per square millimetre of cross section, counts of myelin sheaths

in nerves taken from cases of subacute combined degeneration were rarely as high as 5,000 per square millimetre, and often much below this level. Reference to Table I clearly shows the poverty in the number of myelin sheaths in the nerves obtained from cases of subacute combined degeneration. It will be seen that a similar diminution in number occurs in the cases of alcoholic neuritis.

TABLE I.

NO.	COUNTS	MEAN	DIAGNOSIS
1 S.	2450		
	2920		
	3600	2990	Subacute combined degeneration of the cord.
2 W.	2160		
	3800	2980	Subacute combined degeneration of the cord.
3 H.	1700		
	4650		
	5000	3783	Subacute combined degeneration of the cord.
4 I.	3700		
	5030	4365	Subacute combined degeneration of the cord.
5 K.	1075	1075	Alcoholic neuritis.
6 H.	2860		
	3190		
	3460	3170	Alcoholic neuritis.
7 P.	5200	5200	Polyneuritis.
8 W.	6300		
	6500		
	7280		
	7870	6988	Hypernephroma.
9 B.	5560		
	7000		
	7260		
	9100		
	9600	7704	Cerebral softening.
10 D.	6600		
	7700		
	7800	7387	Hemimyoclonus.
11 B.	6400		
	6900		
	7200		
	7400		
	8900	7760	Cerebellar tumour.
12 F.	7800		
	8400		
	8750		
	9010		
	9050	8602	Pituitary tumour.

On microscopical examination the nerve bundles of the cases of subacute combined degeneration showed some separation of the nerve from its perineurium, and the appearance of fairly wide clefts in the substance of the bundles. This was also observed in nerves from normal subjects, but not to the same degree. It was obvious that this might result either from loss of nerve tissue, or from distension of the perineurium by œdema. In the latter case the reduction in the number of the myelin sheaths per square millimetre might be more apparent than real, although care was taken to exclude empty spaces under the perineurium from the planimetric measurements of the area of nerve examined.

It was therefore considered advisable to have some criterion other than the number of myelin sheaths per square millimetre in assessing the presence and degree of degeneration in these nerves. Accordingly an attempt was made to estimate the proportion of myelin sheaths of different sizes in this nerve obtained from cases of subacute combined

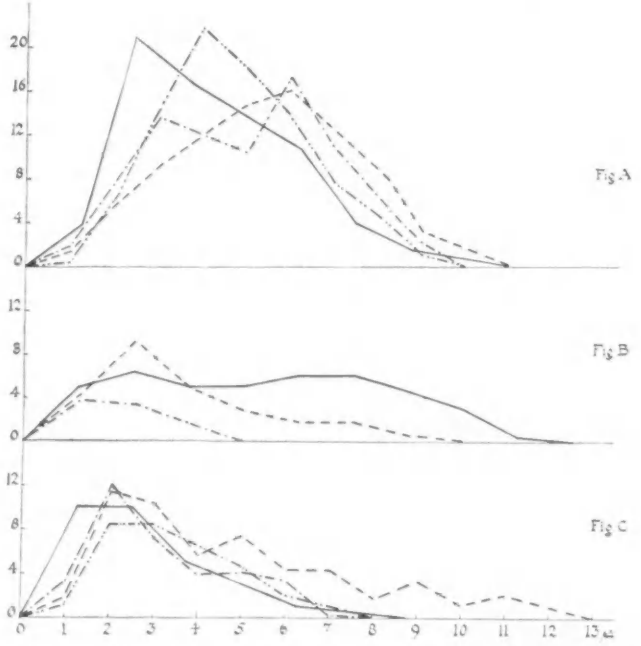

FIG. 1.—Curves of the number of myelin sheaths per sq. mm. in the peripheral nerves from normals, A; in peripheral neuritis, B; and from patients with subacute combined degeneration of the cord C.

B. — . — Case 5.
— — — Case 6.
—— Case 7.
C. — . — Case 1.
— . . — Case 2.
—— Case 3.
— — Case 4.

Ordinates represent number of myelin sheaths in hundreds. Abscissæ represent size of fibres in μ.

degeneration and polyneuritis as well as from controls. Approximate measurements of the diameter of the myelin sheaths in multiples of 1μ were made, and the numbers were then tabulated according to size. The proportion of myelin sheaths of each size was then calculated as a

percentage of those in the whole nerve bundle. These percentages, corrected to the number of myelin sheaths per square millimetre, were taken to give an approximate estimate of the number at each micron of diameter per square millimetre of the cross section of the nerve. When the counts were charted as curves it was found that, whereas the normal nerves contained myelin sheaths ranging from 1 to 10 μ in diameter, with a preponderance of those between 3 and 6 μ, the nerves from cases of subacute combined degeneration contained very few sheaths of over 8 μ, with the great majority under 4 μ (fig. 1). It appeared, therefore, that either the larger myelinated fibres had suffered more than the smaller, or that there was a general reduction in size as well as in number of myelin sheaths. In the nerve obtained from the only post mortem case of subacute combined degeneration a similar preponderance of small myelin sheaths was found; but there were in this nerve a certain number of larger myelin sheaths, some of which measured up to 12 μ. It was noteworthy, in this case, that many of the myelin sheaths, instead of appearing as clear cut circles, presented a double contour or were filled up with darkly-stained material. Longitudinal sections of this nerve showed a considerable amount of beading and irregularity of contour of the myelin sheaths. It is important to note that, in this case, the course of the disease had been rapid, the first symptoms appearing seven months before death, and leading to a bed-ridden condition six weeks before death, which was due to embolism of the pulmonary artery. A similar appearance was seen in the nerve from the case of acute infective polyneuritis of six weeks' duration (Case 7). In the nerve of this case large myelin sheaths up to 12 μ were found, and considerable Wallerian degeneration of individual myelinated fibres was seen in longitudinal sections of the nerve. The similarity of the appearance in the nerves of these two cases suggest that the abnormally large circles, seen in cross section of both nerves, represented swellings of the sheath on rapidly degenerating nerves. It was unlikely to be the result of post-mortem autolysis as no other post-mortem material showed a similar change. The curves plotted from the nerves of cases of subacute combined degeneration were remarkably uniform except for that obtained from this post-mortem case. Curves of very similar type were obtained from two cases of alcoholic neuritis. In one of these there were so few myelin sheaths in some of the nerve bundles, and those present stained so poorly, that it was very difficult to make accurate measurements and counts; the curve charted is taken from the least affected bundle in the section.

Discussion.

The great difference in measurements as well as in counts of myelin sheaths in the nerves of cases of subacute combined degeneration of the cord from those found in normal nerves may be accepted as evidence that there is a true degeneration of the peripheral nerves in this disease. As to the nature of this degeneration it has not been possible to form any definite opinion. The nerves examined by the Gros-Bielschowsky method have shown neither reduction in number, nor an alteration in the appearance of nerve fibres. It therefore seems unlikely that the axons are affected to any appreciable degree. Except in the rapidly fatal case of subacute combined degeneration of the cord to which reference has been made, there was very little abnormality in the contour of the myelin sheaths as seen in longitudinal sections and nothing was ever seen suggesting Wallerian degeneration. Nor is there any reference in the literature to the presence of Wallerian degeneration in subacute combined degeneration of the cord. On the other hand the preponderance of myelin sheaths of small size, as well as the poor staining of many of the myelin sheaths as compared with those in normal nerves, suggest that in subacute combined degeneration the nerve fibres suffer a general impoverishment of myelin. No doubt in severe and rapidly progressive cases Wallerian degeneration of individual fibres may occur, but this must be exceptional.

It has been stated that the appearance in the osmic acid sections might be interpreted as indicating œdema of the fine nerve bundles. That œdema of nerves does occur is known, and it is the rule in many forms of polyneuritis. The presence of œdema in the nerves of cases of subacute combined degeneration, if established, would therefore confirm rather than disprove the view that lesions of peripheral nerves are present in this disease. However, no definite evidence of œdema was found in celloidin sections of the peripheral nerves in any case of this series, although the Weigert-Pal sections of these nerves gave evidence of considerable loss of myelin sheaths. It is therefore not possible to explain these results on the basis of œdema of the peripheral nerves.

Summary.

A. Peripheral nerves from normal people, from cases of subacute combined degeneration of the cord, and cases of neuritis have been compared microscopically.

B. It has been shown that the myelin sheaths are reduced in number in the nerves of patients with subacute combined degeneration, and that

the reduction is of the same type, but not of the same degree, as that found in alcoholic neuritis.

C. The reduction in the number of myelin sheaths affects all sizes, but preponderates among those of large size.

It is a pleasure to express our thanks to our colleagues for permission to record these findings in patients who were under their care. To Mr. Harvey Jackson we are indebted for the skilful manner in which he removed the peripheral nerves under local anæsthesia. This work was carried out on behalf of the Medical Research Council.

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APPENDIX.

Case Histories.

Case 1.—S., male, aged 58, admitted under the care of the late Dr. Collier. He complained of tingling in the fingers for one year. Three months previous to admission he felt weak in his legs and the feet felt numb. On examination he was pale and sallow. There was no abnormality of the cranial nerves. The power of the arms and legs was good and no wasting was present. There was a striking inability to perform fine movements with accuracy in the hands, and he was ataxic in his gait. The arm and leg reflexes were normal. The plantar responses were extensor in type. There was a definite glove-and-stocking distribution of raised threshold to pin-prick and cotton wool. Vibration was lost in the legs. The cerebrospinal fluid was normal. Gastric analysis following histamin showed a complete absence of free HCl. The blood examination was as follows: red blood cells, 2,850,000; hæmoglobin, 92 per cent.; colour index, 1·6. The Price-Jones curve was shifted to the right. A good reticulocyte response was obtained following the administration of campolon.

Case 2.—W., male, aged 44. Nine years previous to admission he had an illness diagnosed as anæmia. From this he rapidly recovered, but one year previous to admission he became easily tired. This was associated with "tingling" of the finger-tips and was followed by a similar sensation in the toes. These subjective sensations spread up the arms to the elbows and up the legs to

the knees. Walking became unsteady and a tight feeling round the waist developed. On examination he was found to be sallow and pale. Examination of the cranial nerves proved negative. Power and range of movement of the arms were good but the fine finger movements were clumsy. A similar condition was found in the legs. There was no wasting or fibrillation in the muscles. The arm reflexes were normal but both the knee and ankle reflexes were absent. The plantar responses were extensor. Sensory examination showed a glove-and-stocking alteration to pin-prick and cotton wool, while appreciation of vibration was lost in the legs. The cerebrospinal fluid was normal. There was no free HCl in the stomach contents after an alcohol meal with histamin subcutaneously. The results of the blood examination were as follows: red blood cells, 2,790,000; hæmoglobin, 92 per cent.; colour index, 1·6. The Price-Jones curve was shifted to the right. After treatment with campolon the reticulocyte count rose to 5 per cent. on the fifth day.

Case 3.—H., male, aged 56. Six years previously he observed that he was unable to feel the floor with his feet. The numbness in the feet progressed, spreading up the legs to below the knee. Two years previous to admission tingling and numbness commenced in the finger tips and spread up to the level of the wrists. At the same time he became unsteady on his feet. On examination he was slightly pale. The cranial nerves were normal. There was no marked wasting of the arms or legs, the power of which was good. The resistance to passive stretching was increased in the quadriceps. Fine movements of both the hands and feet were clumsily performed. The arm reflexes were brisk as were also the knee-jerks. The ankle-jerks were absent. The plantar responses were extensor. There was slight diminution to pin-prick over the digits of all four limbs, while vibration sense was lost in the legs. The cerebrospinal fluid was normal. Examination of the blood gave: red blood cells, 3,140,000; hæmoglobin, 82·3 per cent.; colour index, 1·3. The Price-Jones curve was shifted to the right. A good reticulocyte response was obtained after the administration of campolon. Gastric analysis showed an entire absence of free HCl after a subcutaneous injection of histamin.

Case 4.—I, female, aged 60, admitted under the care of Dr. Grainger Stewart. Seven months previous to admission, tingling and numbness commenced in the finger tips. There was little progress of symptoms till six weeks before admission, when the legs became weak and she had to take to bed fourteen days later. Associated with the weakness of the legs there was a sensation of "grit" in the soles. On admission, owing to her mental instability, the examination of the nervous system was undertaken with difficulty. There was no gross disturbance of function of the cranial nerves. There was no wasting of the arms or legs, all of which exhibited good power. The arm reflexes were normal; the knee and ankle jerks were very brisk, with ankle clonus. The plantar responses were extensor. The threshold for pain was raised in the legs and sense of position was very defective. There were 3,910,000 red blood cells with 93 per cent. of hæmoglobin in the blood,

PLATE XIX.

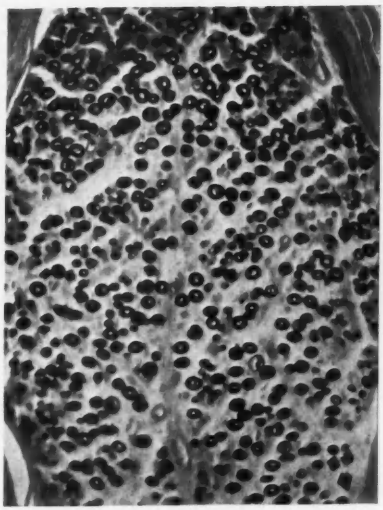

FIG. 2.

FIG. 3.

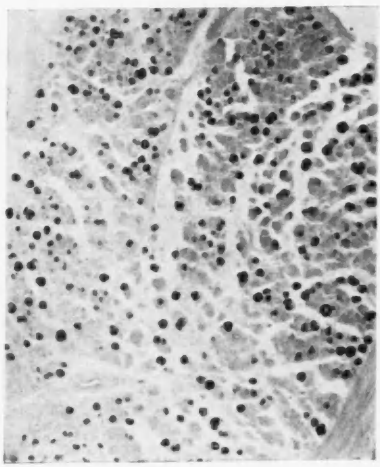

FIG. 4.

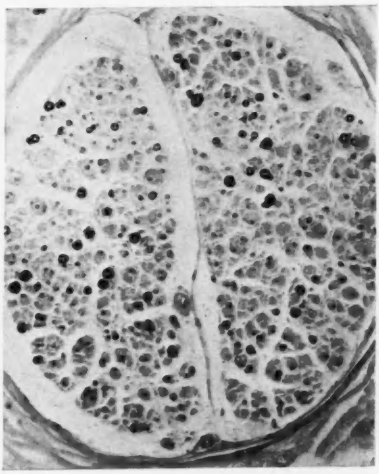

FIG. 5.

FIG 2.—Peripheral nerve from normal, stained with osmic acid. × 200.
FIG. 3.—Peripheral nerve from Case 6 of alcoholic neuritis, stained with osmic acid. × 200.
FIG. 4.—Peripheral nerve from Case 2 of subacute combined degeneration of the cord, stained with osmic acid. × 200.
FIG. 5.—Peripheral nerve from Case 3 of subacute combined degeneration of the cord, stained with osmic acid. × 200.

To illustrate paper by J. G. Greenfield and E. Arnold Carmichael.

giving a colour index of 1·2. Halometric readings indicated a halo of 8·1 μ. She rapidly went downhill and died fifteen days after admission. Post-mortem findings confirmed the diagnosis of subacute combined degeneration of the cord.

Case 5.—K., female, aged 35. For some years she had taken large quantities of wine daily as well as whiskey and beer. Seven months previous to admission she complained of pain in the soles of the feet and cramp in the calves, and during the last six months had been unable to walk. Two months previous to hospital treatment she developed weakness in both hands, and recently had had a very considerable loss of memory. On examination there was a fine irregular nystagmus on lateral deviation of the eyes. There was marked wasting of both forearm and hand muscles with great weakness. The legs were wasted below the knees and bilateral drop-foot was present. All the deep reflexes were absent and no plantar responses were obtained. The muscles of the forearms and calves were exceedingly tender and there was an associated glove-and-stocking anæsthesia to pin-prick. The protein content of the cerebrospinal fluid was 110 mg., otherwise the fluid was normal. The blood examination gave normal results. On appropriate treatment she made a good recovery, the tendon reflexes returning in the arms.

Case 6.—H., male, aged 62, admitted under the care of Dr. Hinds Howell. As manager of a licensed victualler's business, he had taken considerable quantities of alcohol. On two previous occasions he had suffered from delirium tremens. One month before admission he went off his food. During the fourteen days immediately preceding his admission, he had become incoherent and mumbling in his speech. Examination was difficult owing to the mental state. No gross defect of function of the cranial nerves was observed. He moved his arms freely, but his legs were flail-like and very tender to pressure. The arm reflexes were present as were the knee-jerks, but the ankle-jerks were absent. No plantar response was obtained. Sensory tests were impossible. The cerebrospinal fluid was normal. He died four days after admission.

Case 7.—P., female, aged 26, admitted under the care of the late Dr. Adie. Six weeks previous to admission she was seized with sharp pains in the legs. Three weeks later she had definite weakness of arms and legs with numbness of the legs up to the calves. At this time she was unable to walk owing to the weakness of her legs. A few days prior to admission she developed difficulty in swallowing and breathing. On examination of the cranial nerves there was weakness of the facial musculature. There was extensive flaccid weakness of all four limbs without any gross wasting. The tendon reflexes were all absent and no plantar responses were obtainable. There was a glove-and-stocking anæsthesia to pin-prick. She died suddenly two days after admission. The post-mortem diagnosis was acute infective polyneuritis with severe degenerative changes, including Wallerian degeneration, in the peripheral nerves.

THE SUBPIAL RESECTION OF THE CORTEX IN THE TREATMENT OF JACKSONIAN EPILEPSY (HORSLEY OPERATION) WITH OBSERVATIONS ON AREAS 4 AND 6.[1]

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THE purpose of this paper is to draw attention to an operation first suggested by Victor Horsley for the treatment of athetosis, which I have found most effective both for this condition and, to an even greater degree, for Jacksonian epilepsy.

In reviewing my cases of Jacksonian epilepsy extending over a period of twenty-five years, I find that I have performed this operation eleven times, and that there were eleven other cases on whom, in the light of my present knowledge, I feel that I should have carried out the same procedure.

Of the eleven cases operated upon, nine are cured, one has had a recurrence, and one died four weeks after the operation, so that in this case it was too early to speak of end-results, but during the time the patient lived, she was free of athetotic movements (Case 1).

The eleven cases that constitute the basis of this report were selected from a series of 189 cases of supposed focal epilepsies, but in this series no cases are included in whom Jacksonian convulsions were due to a brain tumour.

Of these 189 cases, 120 were discarded because of insufficient evidence that would justify the diagnosis of focal epilepsy. This conclusion was reached after thorough examination and, whenever possible, observation of the convulsions themselves by a trained observer, either a doctor or a nurse. The remaining sixty-nine cases were operated upon, and may be divided into three groups :—

First group.—Eleven cases of typical Jacksonian convulsions with extensive cortical degeneration.

Second group.—Nineteen cases of typical Jacksonian convulsions with definite focal scars.

Third group.—Thirty-nine cases in whom at operation no gross pathological lesion could be seen.

[1] Read at the Meeting of the Second International Neurological Congress, London, England, July 29 to August 2, 1935.

In the first group, nothing was accomplished by operation because the entire or greater portion of the cortex was involved. The degeneration was very extensive, often containing huge degenerative cysts with areas of yellow gelatinous tissue. Most of these patients, besides having convulsions, showed mental deterioration.

In the second group, operation had to be very radical in order to remove the scar completely and, in several instances, the resection was carried down into the ventricle according to the suggestion of Foerster.

In the third group (thirty-nine cases) no pathological lesion could be seen grossly at operation, nor did subsequent histological study of the cortex, in those cases in which some of it was removed, show any abnormality.

This is the group of which I particularly wish to speak. In eleven of these cases, in whom the convulsions were definitely focal, I did a subpial resection of the cortex according to the method used by Victor Horsley and described by him in his Linacre Lecture in 1909. By this procedure it is possible to remove accurately an isolated convolution without encroaching upon a neighbouring area. On the other hand, if the resection of the cortex is undertaken through the intact pia and its intact vessels, it is impossible, in man, accurately to isolate and remove one convolution. In the remaining twenty-eight cases, I did not attempt this procedure. When I found no gross evidence of cortical abnormality, I hesitated to do this unless I was absolutely certain that I was dealing with a true Jacksonian convulsion. In each of these patients, it is true, the convulsions always had the same pattern, but they spread so rapidly and became general that, in the presence of a normal-looking cortex, I was uncertain whether I was justified in considering the convulsion a true focal one. In eleven of these twenty-eight cases, as I have reviewed them recently, in the light of our results I feel I was too conservative and should have done a subpial resection. I had not realized until I analysed these cases for this paper that in those in which I had resected the cortex, the convulsions had been stopped in all but one instance. Three of the patients who were operated upon for local athetosis had athetotic movements identical with those described in Horsley's case, which I was fortunate enough to see while working with him. In all three of these patients (Cases 1, 4, 7) the athetosis was stopped, but, as one patient died four weeks later following another operation, the period of observation was too short to know what the final outcome would have been.

In carrying out the resection of a convolution, it is all-important to

remove the entire centre, arm or leg, as the case may be. In three of my cases the arm was not completely paralysed after the first operation (Cases 2, 3 and 7); therefore I reoperated and removed a larger area. In all three instances I found at the second operation, upon stimulation of the cortex, that I had left part of the arm centre. The histological examination of the areas removed was made for me by Professor James Lee O'Leary, of the Department of Cytology, of Washington University, who found that all but one of the specimens were motor cortex, Area F A gamma, the term applied to it by Economo and so designated because it contains some Betz cells.

In 8 of these 11 cases the convulsions began with a movement in either the arm or leg. The area removed was what is generally spoken of to-day as Area 4. In one case the convulsions definitely were preceded by a sensory aura in the hand, and in this case I removed the post-central gyrus opposite the arm centre. Nine of the ten patients have been free from convulsions; the one who had his post-central gyrus removed has been well for eleven years, and, during the past five or six years, has carried on his work as Professor of Physiology in one of our medical schools.

These cases in which the cortex looked normal to the naked eye and showed no demonstrable pathological changes have given us an unusual opportunity to observe the change in the cortex that occurs just before a convulsion begins. It has happened in many instances that, while searching for a centre with the electric current, we set off a convulsion. Over and over again I have been able to warn my anæsthetist that a convulsion was starting because of the change in the colour of the cortex. This change has invariably been an hyperæmia. Only once have I seen the preliminary pallor which, it has been claimed by some neurosurgeons, is the first observable change that occurs when a convulsion starts (Case 7). Formerly we used a bipolar electrode with a faradic current, but in the last few years have followed the suggestion of Foerster and have used unipolar stimulation with the direct current. The single shocks have the advantage, as he pointed out, of enabling one more accurately to outline a centre without exhausting or irritating it unduly. When a centre receives too much stimulation it becomes hyperactive and convulsions are initiated which obscure the picture and prevent an accurate ablation of the cortical centre.

These cases of resection have given us an opportunity of checking an important physiological question that is still somewhat unsettled, namely, the difference between the loss of function resulting from the removal

of the precentral gyrus as compared with removal of the intermediate precentral gyrus, in other words Area 4 and Area 6. In this series Area 4 was removed ten times. Where a complete paralysis resulted, the length of time before the extremity recovered varied considerably. Usually movements began to return in a week or ten days, while, in a few cases, recovery was much slower. In one patient only slight elbow movements had returned at the end of five weeks. In only one case in this series was there a flaccid paralysis at any time after operation. The grasp reflex was tested in only one or two cases who had been operated upon in recent years, but in none was it found to be present. The absence of this reflex would be in accordance with Fulton's idea of the function of the premotor cortex, but our results do not support his contention that there is, at first, a flaccid paralysis following a removal of the motor cortex.

As only one convolution was removed in each case, we may conclude that the precentral convolution varies in the number of efferent impulses to which it gives rise; thus, if an adjacent convolution contains more efferent fibres earlier recovery may be expected. In regard to the extent of recovery of function, it was invariably observed that recovery of the fingers was much less complete than that of the shoulder, elbow and wrist. Concerning the extent and type of sensory disturbance following removal of Area 4, it was noted in several instances that there was some disturbance in accurate localization, loss of accuracy in recognizing compass points, and what I like to call incomplete astereognosis, due, I believe, to the sensory disturbance. To say that a patient has true astereognosis, there must be no other evidence of a sensory disturbance. I have seen this occasionally, but, in my experience, a pure astereognosis is rare.

Comparing the results in these cases with the results in the cases of wide excisions of scars, we find that where no scar was present the results are distinctly better. Only ten of the nineteen cases of scar excision have been without convulsions for a number of years. Some of the other nine cases have had a return of their convulsions, and some, unfortunately, have been lost sight of.

To speak of a patient who has had Jacksonian epilepsy as cured is an unwarranted statement, for we all know that patients may be free from convulsions for a long time, a number of years, and then the convulsions may recur as a bolt out of the blue. Only those patients may truly be said to be cured who, up to the time of their death from some other cause, years later, have been free of convulsions.

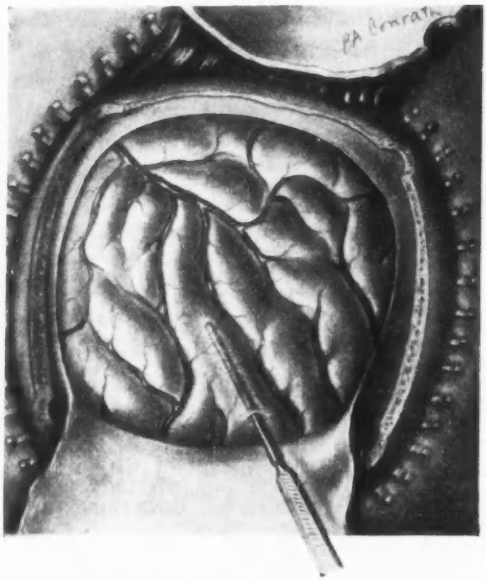

FIG. 1.—Method of freeing the pia.

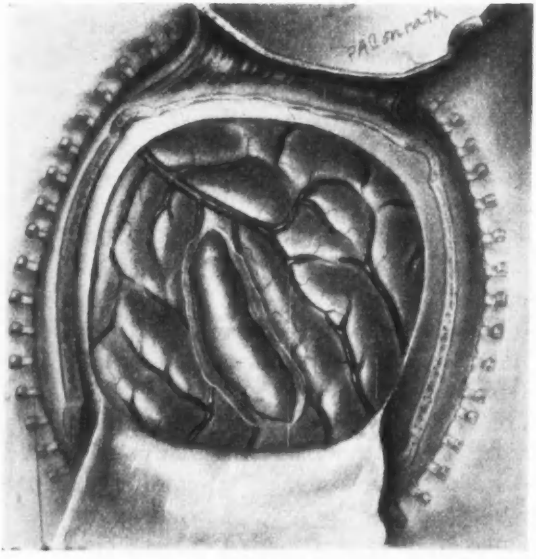

FIG. 2.—The convolution completely freed after the pia arachnoid has been pushed back with cotton pledgets.

It requires a little courage, I have found, to remove what appears to be a normal-looking cortex; but in the light of the experience herein cited, if I am convinced that I am dealing with a true Jacksonian epilepsy, I now have no hesitation in carrying out a subpial resection of the cortex. This procedure I have designated the Horsley operation.

Case 1.—E. F., aged 17, January 11, 1912, Barnes Hospital, No. 149.

At the age of 5 the patient had pertussis and following this developed athetosis in the right upper extremity and to some extent in the lower. The entire right arm and hand were in constant motion. At times the movements

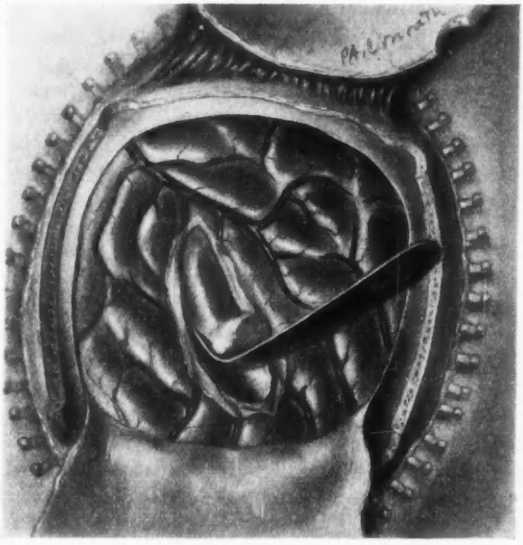

FIG. 3.—Removal of the convolution after the pia arachnoid has been pushed back. This is an absolutely bloodless procedure.

became very violent. Reflexes were not exaggerated. There was also movement of the right leg but not as marked.

Operation January 23, 1912, under ether anæsthesia. A flap was turned down on the left side. Subpial resection of the arm centre was carried out. The arm, following this, was completely flaccid. Reflexes were not elicited. Athetoid movements ceased.

The patient was so pleased with the result that she requested something be done to stop the movements of her leg. Because of the location of the leg centre under the longitudinal sinus and the difficulty of exposing it, as well as because of a discussion to the effect that posterior root section would

stop athetosis just as cortical excision did, on February 15, 1912, a laminectomy was done under ether anæsthesia, and the posterior root of the second, third, and fifth lumbar and the second sacral were cut. When the patient recovered from the anæsthesia, the convulsive movements of the leg were exactly as before operation. The patient developed an infection and died of a meningitis two days later.

Case 2.—W. J., aged 29, September 18, 1915, Barnes Hospital, No. 2350.

Complaint: Convulsions present for four years. Examination was practically negative. Reflexes before operation were normal with normal plantar responses. Four attacks were seen in the hospital which began with twitching in the left hand and then spread; therefore, operation was decided upon. The Wassermann reaction was negative.

Operation October 6, 1915, under ether anæsthesia. The arm centre was identified with the faradic current. The pia was split and the cortex excised. Patient had several post-operative convulsions, but there was no weakness of the left hand. Evidently the operation did not remove enough of the cortex, so the patient was re-operated upon six days later. On restimulating it was found that below the area of excision, there was a response by contraction of the face, and above this there was a response from the hand, forearm, and shoulder. This area was excised subpially.

The left hand became weaker after operation. Dynamometer on October 14, left 75, right 115; on October 18, left 90, right 115. There are no details in the post-operative notes regarding movement of fingers as compared with the rest of the arm. After a week the hand was getting stronger. A month later the left hand had regained its strength practically completely.

Case 3.—C. T., aged 27, May to November, 1917, Barnes Hospital, Nos. 4181, 4654, and 4707.

Present illness: Six months before admission the patient was kicked in the head on the left side by a mule. He was unconscious and was operated upon for compound fracture of the skull. He had a convulsion the night after the accident and then three months later began to have convulsions which commenced in the thumb.

The patient on examination had a partial motor aphasia, slight cortical facial weakness and normal reflexes. Because of the epilepsy he was operated upon on May 23, 1917, under ether anæsthesia. Adhesions were freed and a fat pad inserted.

The attacks were not relieved; therefore the patient was readmitted in October, 1917, still having convulsions. Operation on October 12 under ether anæsthesia. Fat pad found densely adherent to the cortex and removed. On account of the dense adhesions it was difficult to identify the precentral gyrus, but an area from which movement of the opposite extremity was obtained was excised by subpial resection. It was impossible to identify the thumb centre.

Following this operation the patient had some indefinite sensory disturbance but no paralysis of the hand, indicating either that the area removed

was not Area four (4) and that the contraction we had obtained upon cortical stimulation was due to spread of the current, or that I had not removed enough of Area four (4).

The patient was therefore readmitted on October 27, 1917. Operation November 5, 1917, under ether anæsthesia. On stimulation it was found that I had not removed the entire precentral gyrus. This was removed, and following this the patient had a complete paralysis of his upper extremity. After four weeks the patient began to move his arm, first the shoulder girdle muscles. A letter received from him a month later stated that movement in his arm had improved and he was now able to move his fingers. No description as to whether the extremity was spastic or flaccid, or the character of the reflexes is available.

Case 4.—G. S., aged 27, April 29, 1920, Barnes Hospital, No. 8715.

Right hemiplegia at age of 8 which developed after an attack of typhoid fever. The lower extremity improved, but the upper extremity developed athetosis. The reflexes in both arm and leg were increased and ankle clonus was very marked; two-point discrimination test indicated no difference between the right and the left arms. When the patient became excited the left arm went into violent athetoid movements. Operation May 3, 1920, under ether anæsthesia. The arm centre was identified as well as the leg and face centres. A subpial resection from the edges of the leg centre down to the face centre was carried out.

Following operation the patient had complete loss of movement of her right arm. The athetoid movements had stopped. There was slight motor speech disturbance for a few days after operation, which had disappeared on the fifth day after operation; it was evidently due to œdema. Two-point discrimination test showed definite disturbance, but there was no other evidence of a sensory loss. The patient was discharged on May 18, 1920; she had begun to move her arm quite well but no athetoid movements recurred.

Case 5.—C. M., aged 15, July 17, 1920, Barnes Hospital, No. 9047.

At the age of 2 years the patient fell 6 ft. striking his head on a nail. At the age of 9½ he had his first convulsion (focal epilepsy). His attacks were observed in the hospital by a nurse. They began with the neck and head being drawn to the left and twitching of the left side of the body beginning in the left arm, then the left leg, and then the convulsion became general. Reflexes in the arm were overactive, with slight weakness of the left side, but no sensory disturbance.

Operation, July 21, 1920, under ether anæsthesia. On opening the dura there was thickening of the arachnoid. The arm centre was located behind the area of arachnoid thickening. The arm centre was not as accurately outlined as I should have wished because of the scar.

After operation there was no weakness of the movements about the shoulder, but there was weakness of the biceps and triceps and all movements in the forearm and fingers disappeared. Two-point discrimination below the elbow was impaired. On July 29 the strength of the left hand was improving.

Movements of the fingers at the time of discharge were still impaired. Patient when last heard from had had no convulsions.

Case 6.—C. W., aged 28, January 29, 1924, Barnes Hospital, No. 17056.

On November 5, 1922, the patient was in an automobile accident and sustained a comminuted fracture of the skull in the right parieto-occipital region. He was operated upon and a subdural clot removed. Nine months after the operation, while on a holiday in the mountains, he had his first convulsion. As he was a physician he was able to observe his attack very carefully. From this time on he had a convulsion every month for four consecutive months. The convulsive seizure was preceded by an aura as if his left forearm felt strange and did not belong to him. The attacks lasted from eight to thirty minutes. There was twitching of the fingers with systematic flexion extension movements. At the end of this time the patient became unconscious, the period of unconsciousness varied from eight to twelve minutes, and was followed by post-epileptic automatism lasting about ten minutes. Large doses of luminal did not control the attacks.

Operation, January 30, 1924, under ether anæsthesia. There was a dense scar between the scalp, bone and site of the old fracture. There was an area 5 by 5 cm. where there was a dense scar attached to the cortex. Cortical stimulation revealed that the motor area was entirely in front of the scar. The entire area involved with the scar was therefore excised, subpial resection being done. Forty-eight hours later the patient had a left facial weakness with flaccidity of the left arm and leg and an ankle clonus. The patient was drowsy and the pulse had dropped to 55. Evidently a clot had formed. On reopening the flap a moderate extradural clot was found, not enough to explain the symptoms. On opening the dura, the site of the cortical excision was filled with a huge blood clot. This was washed out and a silver clip put on a small bleeding spot.

The patient had one convulsive movement of the left hand two days after the second operation, then made an uneventful recovery. For the past five years the patient has held the Chair of Professor of Physiology at a Mid-Western medical school. He has never had a return of symptoms, either sensory or motor.

Case 7.—A. W., aged 22, October 12, 1928, Barnes Hospital, No. 17388.

Patient sustained a birth injury and from a few days after birth had athetoid movements of the right hand and forearm. She only began to walk at the age of 2, and talking was somewhat retarded. At the age of 12 she had her first convulsion which involved the face and the right arm. It was followed by a period of unconsciousness which lasted about an hour. A typical convulsion was described as beginning with a peculiar drawing sensation in the right side of the face, followed by drawing of the mouth to the right, quivering of the right arm and then tonic contraction of the arm and hand, the leg was very slightly involved. The patient frequently bit her tongue. The patient then combined athetotic movements of the right hand with typical Jacksonian convulsions beginning in the face and spreading to the hand.

Operation, October 15, 1928, under local anæsthesia. A left-sided craniotomy was carried out. It was somewhat difficult to locate the arm centre with the faradic current; more stimulation than usual had to be used. Finally the patient had a general convulsion. The cortex became typically pale and then, as the convulsion advanced, hyperæmic. Subpial resection of the cortex was carried out, extending from the abdominal centre right down to and including the wrist centre.

Following the operation the arm was spastic but not completely paralysed. Therefore four days later the wound was reopened under local anæsthesia, and on stimulation part of the arm centre was found still intact. This was excised by the same technique. Following this operation there was complete paralysis of the arm, forearm and hand. The hand was spastic. Occasional slight athetotic movements were still noted at the time of discharge. A letter from the patient a year later stated that she had been free of convulsions for a year, but following fright over a fire she had had one convulsion.

Case 8.—G. S., aged 18, May 8, 1931, Barnes Hospital, No. 29510.

Ten years ago the patient had a severe fracture of the skull. He was operated upon three times for the skull defect. For the past seven years he has had focal convulsions beginning in the right arm and spreading to the leg; the face was never involved. Following the convulsions the patient has weakness of the right upper extremity and of the toes. No sensory disturbances were present. No weakness existed between attacks. At the time of admission the patient was practically in a state of status epilepticus, having convulsions of the right arm every few minutes. It was impossible to control these with hypnotics. Therefore cortical excision was decided upon.

Operation, May 12, 1931, under local anæsthesia. On location of the arm centre with the galvanic current repeated convulsions were started. The cortex looked normal. The face centre was located higher than usual. Subpial resection of the cortex was not as neat a job because of the numerous vessels which had to be coagulated. At the end of the operation the patient was unable to move either his arm or his leg. The morning after operation the patient has some movement of his leg, but no movement of his arm whatever. He made an uneventful recovery. Occasionally he had a peculiar feeling in the right arm, but no convulsive movements were noted. At the time of discharge on May 30, there was no return of function in the arm. A note a year later stated that the boy used his hand perfectly but said that it was "dumb." He had no attacks since the operation. Occasionally he had peculiar sensations in his right hand which he described as twitching but no convulsive movements noted.

Subsequent history: One year later the patient began to have convulsions which have slowly become more frequent, and about April, 1935, he began to have increasing weakness of his arm and speech difficulty.

Patient was last seen in June, 1935. At this time he had slight convulsive twitchings of his right arm but no true convulsions; there was some hesitation of speech which is the residue of an old sensory aphasia.

Case 9.—L. F., aged 52, June 12, 1933, Barnes Hospital, No. 38823.

Patient was shot in the head one and a half years ago. One year later he developed right-sided convulsions and had six in all. Physical examination revealed right-sided hemiparesis, exaggerated reflexes in the arm, particularly in the wrist, slight ankle clonus, Babinski and Oppenheim responses, a suggestion of patellar clonus on the right, and the right abdominal reflex was less than the left. The convulsion was typically Jacksonian, beginning in the right hand and arm and extending to the shoulder. From the description it is not clear whether the sequence is arm to face or arm to leg. No sensory disturbance was present.

Operation, June 15, 1933, under local anæsthesia. The arm centre was located with the galvanic current. Stimulation started a convulsion. Subpial resection of the arm centre was carried out. All the rest of the scar tissue was then excised with the electric knife down to normal brain tissue. The ventricle was not opened.

There was complete paralysis of the hand but some movements in the arm and slight right facial weakness. At discharge on July 4, 1933, there was no return of movement in the hand, but movements of the arm were stronger. No evidence of spasticity in the arm. Patient has had no convulsions since discharge.

Case 10.—L. L., aged 40, May 10, 1934, Barnes Hospital, No. 43337.

Past history negative. For the past three months the patient has had Jacksonian convulsions involving the left arm and leg. Shortly before admission he began to limp and had weakness of the left leg and foot. Reflexes in both arms were perfectly normal. Neurological examination revealed no disease. A tumour, possibly an angioma, of the cortex was considered as a possibility. The cerebrospinal fluid was normal. Repeated attacks observed in the hospital always began in the left arm.

Operation, May 12, 1934. Under avertin a flap was turned down on the right side, the cortex looked normal. It was impossible to locate the arm centre with the galvanic current so that the faradic current had to be used. It was then possible to outline Area 4. A subpial resection of the cortex was carried out.

Following operation there was complete loss of movement of the arm and slight involvement of the flexion movements at the hip, but otherwise the leg was not involved. Reflexes in the left arm were perfectly normal; no flaccidity was noted. For three weeks after operation the patient had no movement in the arm whatever, but on June 5, flexor movements of the fingers and elbow were first obtained. The flexor movements increased in strength, the extensor movements were slow in recovering. At the time of discharge the patient had recovered only moderate use of his extremities. Since discharge there have been no convulsions. Power of the arm has never become normal, especially of the hand.

Case 11.—W. A., aged 11, October 4, 1934, St. Louis Children's Hospital, No. K-2199.

Jacksonian epilepsy beginning in the right hand with sensory aura and involving the right arm since the age of 3. The attacks were checked by luminal. Lately convulsions have been more frequent and more severe, but without loss of consciousness. Recently slight hemiparesis, mostly of the right upper extremity, appeared. Sensation was normal, including two-point discrimination on both sides. Patient walks with a slight hemiplegic gait. Evidently a focal epilepsy involving the arm centre.

Operation, October 10, 1934, under avertin anæsthesia. A broadened post-central convolution was found which was harder than normal but looked like normal brain tissue. This broadened convolution was found to contain the arm centre and a subpial resection was done.

After operation all movements of the upper extremity were absent except shrugging the shoulder. Biceps and triceps reflexes were normal; there was slight facial weakness, but no involvement of the leg. On October 13 the wound was reopened because of a moderate-sized extra-dural clot. The patient was discharged on October 28. At discharge there was poor movement in the right upper extremity; the greatest difficulty was in the extension of the wrist and extension of the fingers. Two months later movement of the arm had markedly improved, but there was still impairment of the finer movements of the fingers.

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Notices of Recent Publications.

Handbuch der Neurologie. Herausgegeben von O. Bumke and O. Foerster. Berlin: Julius Springer. 1935.

The aim of the Editors of this system of neurology is to furnish a comprehensive and up-to-date series of volumes which will include all our latest knowledge in every branch of neurology. They have succeeded in collecting a noteworthy band of contributors, mostly from Germany it is true, but many from other countries, who can write authoritatively on the subjects allotted to them. The material is ready for publication, and it is stated that volumes will appear each month until the whole system is complete at the end of 1936. There will be in all seventeen volumes, and the price at time of publication will be 1260 RM., which will be considerably increased later. The cost is certainly high, but the system promises to be, for several years at least, the most complete work available in any language. The volumes now available for review are splendidly produced, the paper is good, the type is clear and legible, and the illustrations are well chosen and excellently reproduced.

Band I.: *Anatomie.* Pp. 1152, with 585 illustrations. Price RM. 120.

The first volume is entirely devoted to the anatomy of the peripheral and central nervous systems. It is thoroughly up to date and certainly includes all available anatomical facts which will be required by the clinical and research neurologist. It is profusely illustrated; there is, in fact, an average of at least one figure for every two pages, and a comprehensive bibliography at the end of each chapter. A very full index of authors and subjects is also provided.

It is impossible to give an adequate review of the contents of this volume, but a list of its subjects and of their authors will serve to indicate its scope. In the first chapter Rose gives an excellent but concise description of the embryology and development of the nervous system, a subject the importance of which is often lost sight of in the study of anatomy and in interpreting the relation of clinical symptoms and structural lesions. M. Bielschowsky deals with the histology of nerve cells and fibres, of the neurologia, and of the blood-vessels and lymph paths, and then defines the general principles of the pathology of these structures. He also discusses the neurone theory, which is more fully treated by Cajal in a later chapter. Alice Rosenstein and Pollok deal respectively with the anatomy of the peripheral nerves and of the spinal cord and brain-stem, Gagel with the anatomy of the cerebellum, Spatz with that of the mid-brain, and Rose with the structure of the cerebral hemispheres. All these chapters are excellent, and as far as can be seen they are as complete as they could be in the pages allotted to them.

In the next chapter Rose describes the structure of the cerebral cortex, in

more detail perhaps than is necessary in a volume of this character. It extends in fact to almost 200 pages, but it is liberally illustrated. Two useful chapters on the blood supply of the cerebral cortex and the distribution of neurologia in the nervous system by Freedom and Schroeder, are followed by one on the macroscopical and microscopical anatomy of the vegetative system by Greving. Before his death Cajal completed his section on the neurone theory and its significance in physiology and pathology. In the final chapter Boeke describes the mode and the principles of regeneration of nerve fibres.

Band VII. Erster Teil. *Humoralpathologie der Nervenkrankheiten.* Pp. 505, with 67 illustrations. Price RM. 82.

The whole of this volume, which has been written by F. Georgi and O. Fischer, is devoted to the pathology of the blood, urine and cerebrospinal fluid in nervous diseases. The first 200 pages deal with the blood and urine in various neurological conditions; the next 100 pages or so with the cerebrospinal fluid. In the latter section the presence in the fluid of ferments, hormones, immune bodies and other substances is fully discussed. The pathological changes, in the cerebrospinal fluid particularly, in all types of nervous diseases are fully described in the last chapter.

Each of these chapters contains an extraordinary wealth of facts and observations, many of which, though important, must be unknown to the ordinary neurologist; each is, in fact, a complete review of the subject with which it deals. There is probably no other single source in which so much information in these subjects can be found so scientifically collected together and so authoritatively correlated. A bibliography of nearly 100 pages and an adequate index make it possible to use this volume as a separate monograph.

Traité de Physiologie Normale et Pathologique: Physiologie Nerveuse. 2me Partie. E. G. Roger et L. Binet. 1935. Paris: Masson et Cie. Pp. 1580, with 275 illustrations. Price fr. 250.

Volume 10, which appears in two parts, completes the system of Physiology which has been edited by Professors Roger and Binet. It is, as the preceding volume which we have already reviewed (vol. 56, p. 343), wholly devoted to the physiology and physiological pathology of the nervous system. Several of its chapters are of outstanding merit and interest, as that by Bremer on the cerebellum and that by Garcin on the functions of the cranial nerves and their disturbances. Probably nowhere are the functions of the vestibular apparatus more clearly and concisely presented than in the latter. There is also an excellent section on the sympathetic and parasympathetic systems, but recent work which has shown the important part played by chemical substances in the activity of these systems is scarcely referred to. Haguenau treats the cerebrospinal fluid on more or less conventional lines, and Logre, in his chapter on psychophysiology, deals almost exclusively with the mental symptoms due to mechanical or chemical damage, and those which develop on a constitutional

basis. The chapters on the conduction and specific functions of the spinal cord and brain-stem are disappointing. Milian's excellent article on the physiology of the skin and its organs contains much valuable information, and H. Pieron's chapter on " le Toucher," that is sensations dependent on cutaneous and proprioceptive stimuli, attains the high level to be expected from its author. The physiology of the special senses is adequately presented in special sections. Froment writes on articulation and speech; the discussion of articulation and its disturbances is excellent. It can hardly be expected that the views of an author on speech and aphasia will receive general approbation, but the author presents his own attitude satisfactorily.

Huntington's Chorea. By JULIA BELL. The Treasury of Human Inheritance, Cambridge University Press, 1934. Vol. IV., " Nervous Diseases and Muscular Dystrophies," Part 1. Pp. 63, with 12 plates. Price 10s.

This study contains a brief account of the symptomatology of Huntington's chorea, a passing reference to its morbid anatomy and an analysis of the information which the author has collected as to its age and sex incidence, its duration and inheritance.

The onset of symptoms is commonest in the fourth decade of life, but the range of years over which the malady may make its first appearance is a wide one. The sex incidence is approximately equal and the duration averages some fourteen years. There is no direct relationship between the severity of the choreiform and of the mental disorder, in some cases the former and in others the latter is the predominant symptom.

The disease behaves as a dominant, being transmitted directly from parent to offspring. 151 pedigrees and histories are given. There is also a comprehensive bibliography of the clinical and pathological literature of the disease.

L'Abolition Isolée du Réflexe Pupillaire d'Adaptation à la Lumière. By A-M. H. LAGRANGE. Paris: Dion et Cie. 1935. Pp. 160. Price 40 francs.

The author undertakes a clinical study of the Argyll-Robertson phenomenon as observed in syphilitic and in non-syphilitic subjects, including in the latter category cases of the so-called " myotonic " pupil.

She confines her discussion to the loss of the light reaction and does not consider the possible significance of the other signs which together make up the syndrome in its complete form, namely, miosis, irregularity and inequality of pupils and atrophic changes in the iris. She refers to the work of Dupuy-Dutemps, who has emphasized the importance of considering all these components in any searching analysis of the syndrome, and who pointed out that the final state of the Argyll-Robertson pupil in long-standing cases of tabes is one of complete immobility. It may be doubted whether our knowledge of

this complex and, so far, unexplained syndrome can be materially advanced until some generalization is found which will satisfactorily embrace all its components. The author completely evades this problem.

Ueber Myotonie. Klinische und erbpathologische Beiträge. Von H. Boeters. Leipzig: Georg Thième. 1935. Pp. 82. Price RM. 5.60.

Boeters gives an extensive synopsis of published papers on myotonia congenita (Thomsen's disease) as well as on myotonia atrophica. The author himself examined twenty patients affected by myotonia and nearly all their relations living in Silesia. He publishes fourteen tables and twenty pedigrees. Like previous authors Boeters thinks the disease is transmitted by dominant heredity. Nisson, himself a member of the Thomsen family, has asserted that Thomsen's disease and myotonia atrophica were fundamentally different affections having nothing in common except myotonic disturbance, but Boeters, like Rosett and others, maintains that both affections are the same. He draws this conclusion, which has not been hitherto accepted by other authors, from having observed in the same families typical cases of both diseases. It would be of interest to know whether detailed examinations were performed (for example of lenses by slit-lamp) in order to make sure that cases considered to be Thomsen's disease were completely free from signs and symptoms considered pathognomic of myotonia atrophica.

Des Réflexes Conditionelles: Etudes de physiologie normale et pathologique. Par G. A. Marinesco et A. Kreindler. Paris: Librarie Félix Alcan. 1935. Pp. 168.

The authors give a general review of the observations and views associated with the name of Pavlov, and they attempt an application of these doctrines to a wide range of psychoneuroses and psychoses, and to the study of disorders of the speech function. This application, although it is illustrated by some clinical reports, is predominantly of a philosophic rather than of a clinical order.

The Autonomic Nervous System: Anatomy, Physiology and Surgical Treatment. By J. C. White. London: Henry Kimpton. 1935. Pp. 386. Price 30s.

The chief interest of this book lies in its detailed account of the various surgical procedures now practised upon the sympathetic system. These are described from the technical and the clinical aspects and the author affords a comprehensive review of the present state of the surgery of the sympathetic system, and of the results so far obtained.

Although theoretical arguments are not lacking to rationalize the ever-increasing number of such interventions, and the steadily growing range of maladies and symptoms for which they are carried out, it appears that in some

instances they are in the nature of "shots in the dark," undertaken hopefully because no other adequate method of relief or cure is available.

Even where the theoretical basis of operation appears sound the results are sometimes profoundly discouraging. The treatment of epilepsy provides a case in point. It has been observed that stimulation of the cervical sympathetic decreases the capillary bed within the brain, while sympathectomy increases it by some 50 per cent. It has also been reported that when the brain is exposed the onset of an epileptic fit is heralded by a local spasm of cortical arteries. It has been argued, therefore, that bilateral cervicothoracic ganglionectomy which effects complete sympathetic denervation of the brain should prevent the occurrence of epileptic fits. White records seventeen cases so treated. In two only of these is it possible to see any remarkable sequence of the operation. The patients were children of the ages of 7 and 14 respectively, and their liability to fits was in each case of short duration. Both have since remained (for three years) free from all fits. But it is doubtful whether anyone familiar with the natural history of the malady, and aware that sometimes in childhood epileptic fits cease spontaneously for a period of years, would venture to find these results as encouraging as does the author, and the reader is left with the impression that greater discrimination in the use of sympathetic surgery might in the end sooner reveal its scope of usefulness, and avert many fruitless operations upon the sick.

Individual Psychology : Medical Pamphlets : Nos. 11A, 12, 13, 14. London : C. W. Daniel. 1934-35. Pp. 55. Price 2s. 6d. each.

This little collection of papers delivered by Alfred Adler and his followers in England is characteristic of what individual psychology has now become, a useful, limited, intellectually unambitious way of dealing with neurotic problems. The outlook of some of the writers is simple to the point of naïveté ; others have a background of philosophic interest, here best propounded by Dr. Leonhard Seif, a typically Adlerian approach to "life philosophy."

Mental Health : Its Principles and Practice. By F. E. HOWARD and F. L. PATRY. New York : Harper and Bros. 1935. Pp. 551. Price 15s.

Mental hygiene is necessarily propagandist, with the result that many of the books dealing with it are vague and enthusiastic, when the reader would prefer them to be concrete. This book, although wordy, is more satisfying to the medical reader. The teaching of Adolf Meyer is presented in it coherently so that the psychiatric part offers an easy but sound introduction to this difficult subject. In the first third of the book sexual and other psychological problems are elucidated from the standpoint of mental hygiene : the remainder is taken up with "ergosiology," or objective psycho-biology, and the methods of recognizing and dealing with deviations from mental health, especially those which occur in children. Educational problems are dealt with more fully than is usual in such works.

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